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Request for grant of a patent

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1. Your reference	RJW/BP5746490
2. Patent application number *(The Patent Office will fill in this part)*	**9901929.1** 28 JAN 1999
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	THE UNIVERSITY OF PORTSMOUTH HIGHER EDUCATION CORPORATION UNIVERSITY HOUSE WINSTON CHURCHILL AVENUE PORTSMOUTH PO1 2UP
Patents ADP number *(if you know it)*	759228001
If the applicant is a corporate body, give the country/state of its incorporation	ENGLAND
4. Title of the invention	COMPOUNDS
5. Name of your agent *(if you have one)*	MEWBURN ELLIS
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	YORK HOUSE 23 KINGSWAY LONDON WC2B 6HP
Patents ADP number *(if you know it)*	109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month /year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

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Continuation sheets of this form	0
Description	212 ✓ 88H
Claim*(s)*	8
Abstract	0
Drawing*(s)*	24 + 24

10. If you are also filing any of the following, state

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	1 ✓
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(Please specify)*	0

11. I/We request the grant of a patent on the basis of this application.

Signature Merrelyn Ellis

Date 28 January 1999

12. Name and daytime telephone number of person to contact in the United Kingdom — ROBERT J WATSON — 0171 240 4405

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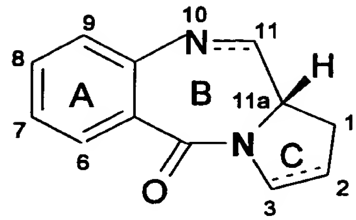
COMPOUNDS

This application has the same text and claims as GB 9818733.9, except for new description pages 210 to 212, and new claims 41 to 43.

The present invention relates to pyrrolobenzodiazepines (PBDs).

Background to the invention

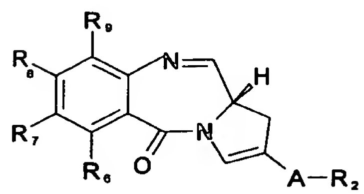
Some pyrrolobenzodiazepines (PBDs) have the ability to recognise and bond to specific sequences of DNA; the preferred sequence is PuGPu. The first PBD antitumour antibiotic, anthramycin, was discovered in 1965 (Leimgruber *et al.*, 1965 *J. Am. Chem. Soc.*, **87**, 5793-5795; Leimgruber *et al.*, 1965 *J. Am. Chem. Soc.*, **87**, 5791-5793). Since then, a number of naturally occurring PBDs have been reported, and over 10 synthetic routes have been developed to a variety of analogues (Thurston *et al.*, 1994 *Chem. Rev.* **1994**, 433-465). Family members include abbeymycin (Hochlowski *et al.*, 1987 *J. Antibiotics*, **40**, 145-148), chicamycin (Konishi *et al.*, 1984 *J. Antibiotics*, **37**, 200-206), DC-81 (Japanese Patent 58-180 487; Thurston *et al.*, 1990, *Chem. Brit.*, **26**, 767-772; Bose *et al.*, 1992 *Tetrahedron*, **48**, 751-758), mazethramycin (Kuminoto *et al.*, 1980 *J. Antibiotics*, **33**, 665-667), neothramycins A and B (Takeuchi *et al.*, 1976 *J. Antibiotics*, **29**, 93-96), porothramycin (Tsunakawa *et al.*, 1988 *J. Antibiotics*, **41**, 1366-1373), prothracarcin (Shimizu *et al*, 1982 *J. Antibiotics*, **29**, 2492-2503; Langley and Thurston, 1987 *J. Org. Chem.*, **52**, 91-97), sibanomicin (DC-102)(Hara *et al.*, 1988 *J. Antibiotics*, **41**, 702-704; Itoh *et al.*, 1988 *J. Antibiotics*, **41**, 1281-1284), sibiromycin (Leber *et al.*, 1988 *J. Am. Chem. Soc.*, **110**, 2992-2993) and tomamycin (Arima *et al.*, 1972 *J. Antibiotics*, **25**, 437-444). PBDs are of the general structure:



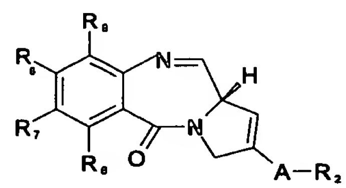
They differ in the number, type and position of substituents, in both their aromatic A rings and pyrrollo C rings, and in the degree of saturation of the C ring. In the B-ring there is either an imine (N=C), a carbinolamine(NH-CH(OH)), or a carbinolamine methyl ether (NH-CH(OMe))at the N10-C11 position which is the electrophilic centre responsible for alkylating DNA. All of the known natural products have an (*S*)-configuration at the chiral C11a position which provides them with a right-handed twist when viewed from the C ring towards the A ring. This gives them the appropriate three-dimensional shape for isohelicity with the minor groove of B-form DNA, leading to a snug fit at the binding site (Kohn, 1975 In *Antibiotics III*. Springer-Verlag, New York, pp. 3-11 ; Hurley and Needham-VanDevanter, 1986 *Acc. Chem. Res.*, **19**, 230-237). Their ability to form an adduct in the minor groove, enables them to interfere with DNA processing, hence their use as antitumour agents.

Disclosure of the invention

A first aspect of the present invention is a compound with the formula **Ia** or **Ib**:



(Ia)



(Ib)

wherein:

A is CH_2, or less preferably a single bond;

R_2 is selected from: R, OH, OR, CO_2H, CO_2R, COH, COR, SO_2R, CN;

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group (i.e. an alkyl group with one or more aryl substituents), preferably of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, preferably of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group;

and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above, or the compound is a dimer with each monomer being the same or different and being of formula **Ia** or **Ib**, where the R_8 groups of the monomers form together a bridge having the formula -X-R'-X- linking the

monomers, where R′ is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings, e.g. benzene or pyridine, and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;
except that in a compound of formula **Ia** when A is a single bond, then R_2 is not $CH=CH(CONH_2)$ or $CH=CH(CONMe_2)$.

If A is a single bond then R_2 is bonded directly to the C-ring of the PBD.

If R is an aryl group, and contains a hetero atom, then R is a heterocyclic group. If R is an alkyl chain, and contains a hetero atom, the hetero atom may be located anywhere in the alkyl chain, e.g. $-O-C_2H_5$, $-CH_2-S-CH_3$, or may form part of or be a functional group e.g. carbonyl, hydroxy.

It is preferred that in a compound of formula **Ia** when A is a single bond, then R_2 is not $CH=CR^AR^B$, where R^A and R^B are independently selected from H, R^C, COR^C, $CONH_2$, $CONHR^C$, $CONR^C{}_2$, cyano or phosphonate, where R^C is an unsubstituted alkyl group having 1 to 4 carbon atoms.

R is preferably selected from a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group, preferably of up to 12 carbon atoms, or an aryl group, preferably of up to 12 carbon atoms, optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is more preferred that R is selected from a

lower alkyl group having 1 to 10 carbon atoms optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is particularly preferred that R is an unsubstituted straight or branched chain alkyl, having 1 to 10, preferably 1 to 6, and more preferably 1 to 4, carbon atoms, e.g. methyl, ethyl, n-propyl, n-butyl or t-butyl.

Alternatively, R_6, R_7, R_9 and, unless the compound is a dimer, R_8 may preferably be independently selected from R groups with the following structural characteristics:

(i) an optionally substituted phenyl group;

(ii) an optionally substituted ethenyl group;

(iii) an ethenyl group conjugated to an electron sink.

The term 'electron sink' means a moiety covalently attached to a compound which is capable of reducing electron density in other parts of the compound. Examples of electron sinks include cyano, carbonyl and ester groups.

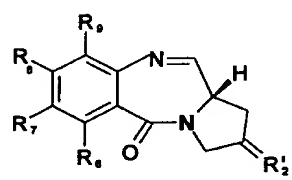
It is preferred that A is CH_2 and/or that R_2 is CO_2H, CO_2R, CH_2OH, or CH_2OR. It is further preferred that R_2 is CO_2Me, $CO_2{}^tBu$, CH_2OH, or CH_2OAc.

R_6, R_7, and R_9, unless the compound is a dimer, R_8 are preferably selected from H and OR, and more particularly H, OMe and OCH_2Ph. It is further preferred that R_7 and, unless the compound is a dimer, R_8 are OR, more preferably OMe or OCH_2Ph, and that R_6 and R_9 are H.

Compounds of the first aspect of the invention are preferably of formula **Ia**.

If the compound of formula **Ia** or **Ib** is a dimer, the dimer bridge may be of the formula $-O-(CH_2)_p-O-$, where p is from 1 to 12, more preferably 3 to 9.

A second aspect of the present invention is a compound with the formula **II**:



(II)

wherein:

R'_2 is selected from: O, CHR''_2, where R''_2 is selected from H, R, CO_2R, COR, CHO, CO_2H, halo;

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group (i.e. an alkyl group with one or more aryl substituents), preferably of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, preferably of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group;

and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above or the compound is a dimer with each monomer being the same or different and being of formula **II**, where the R_8 groups of the monomers form together a bridge having the formula -X-R'-X- linking the monomers, where R' is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings, e.g. benzene or pyridine, and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;

except that:

(i) when R'_2 is CH-Et, and R_6, R_8 and R_9 are H, R_7 is not sibirosamine pyranoside; and

(ii) when R'_2 is CH-Me, and R_6 and R_9 are H, R_7 and R_8 are not both H or both OMe, or OMe and OH respectively.

If R is an aryl group, and contains a hetero atom, then R is a heterocyclic group. If R is an alkyl chain, and contains a hetero atom, the hetero atom may be located anywhere in the alkyl chain, e.g. $-O-C_2H_5$, $-CH_2-S-CH_3$, or may form part of or be a functional group e.g. carbonyl, hydroxy.

R is preferably selected from a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group, preferably of up to 12 carbon atoms, or an aryl group, preferably of up to 12 carbon atoms, optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is more preferred that R is selected from a lower alkyl group having 1 to 10 carbon atoms optionally

substituted by one or more halo, hydroxy, amino, or nitro groups. It is particularly preferred that R is an unsubstituted straight or branched chain alkyl, having 1 to 10, preferably 1 to 6, and more preferably 1 to 4, carbon atoms, e.g. methyl, ethyl, n-propyl, n-butyl or t-butyl.

Alternatively, R_6, R_7 and R_9 and, unless the compound is a dimer, R_8 may preferably be independently selected from R groups with the following structural characteristics:

(i) an optionally substituted phenyl group;

(ii) an optionally substituted ethenyl group;

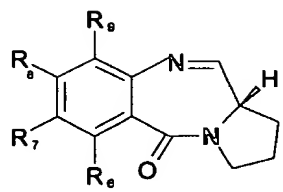
(iii) an ethenyl group conjugated to an electron sink.

It is preferred that R'_2 is O, CH_2 or $CHCH_3$.

R_6, R_7, and R_9 and, unless the compound is a dimer, R_8 are preferably selected from H and OR and a halogen atom, and more particularly H, OMe and OCH_2Ph, and I. It is further preferred that R_7 and, unless the compound is a dimer, R_8 are OR or a halogen atom, more preferably OMe, OCH_2Ph or I, and that R_6 and R_9 are H.

If the compound of formula **II** is a dimer, the dimer bridge may be of the formula $-O-(CH_2)_p-O-$, where p is from 1 to 12, more preferably 3 to 9.

A third aspect of the present invention is a compound with the formula **III**:



(III)

wherein:

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group (i.e. an alkyl group with one or more aryl substituents), preferably of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, preferably of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group; and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above or the compound is a dimer with each monomer being the same or different and being of formula **III**, where the R_8 groups of the monomer form together a bridge having the formula -X-R'-X- linking the monomers, where R' is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings, e.g. benzene or pyridine, and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;

wherein at least one of R_6, R_7, R_8 and R_9 are not H;

except that:

(i) when R_6 and R_9 are H, R_7 and R_8 are not both OMe, OMe and OBn respectively, or OMe and OH respectively;

(ii) when R_6 and R_7 are H, R_8 and R_9 are not Me and OH respectively;

(iii) when three of R_6, R_7, R_8 and R_9 are H, the other is not Me;

(iv) when R_6, R_7, and R_8 are H, R_9 is not OMe;

(v) when R_6, R_8 and R_9 are H, R_7 is not OMe; and

(vi) when R_6, and R_9 are H and R_7 is OMe, the compound is not a dimer.

If R is an aryl group, and contains a hetero atom, then R is a heterocyclic group. If R is an alkyl chain, and contains a hetero atom, the hetero atom may be located anywhere in the alkyl chain, e.g. $-O-C_2H_5$, $-CH_2-S-CH_3$, or may form part of or be a functional group e.g. carbonyl, hydroxy.

R is preferably selected from a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group, preferably of up to 12 carbon atoms, or an aryl group, preferably of up to 12 carbon atoms, optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is more preferred that R is selected from a lower alkyl group having 1 to 10 carbon atoms optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is particularly preferred that R is an unsubstituted straight or branched chain alkyl, having 1 to 10, preferably 1 to 6, and more preferably 1 to 4, carbon atoms, e.g. methyl, ethyl, n-propyl, n-butyl or t-butyl.

Alternatively, R_6, R_7 and R_9 and, unless the compound is a dimer, R_8, may preferably be independently selected from R groups with the following structural characteristics:

(i) an optionally substituted phenyl group;

(ii) an optionally substituted ethenyl group;

(iii) an ethenyl group conjugated to an electron sink.

It is preferred that either:

(i) only one of R_6, R_7, R_8 and R_9 is H; or

(ii) at least one of R_6, R_7, R_8, and R_9 is NH_2; or

(iii) at least one of R_6, R_7, R_8 and R_9 is an aryl group, preferably of up to 12 carbon atoms, which is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally contains one or more hetero atoms which may form part of, or be, a functional group.

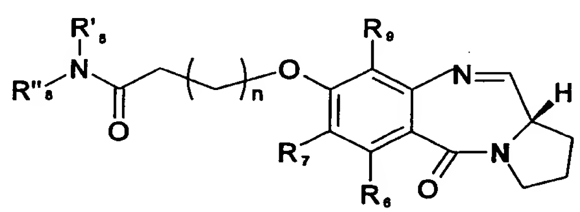
If only one of R_6, R_7, R_8 and R_9, it is further preferred that the A-ring substituents (i.e. those of R_6, R_7, R_9 and, unless the compound is a dimer, R_8 which are not H) are OR, and are more preferably selected from OMe, and OBn.

If at least one of R_6, R_7, R_8 and R_9 is an aryl group, preferably of up to 12 carbon atoms, which is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally contains one or more hetero atoms which may form part of, or be, a functional group, it is further preferred that at least one of R_6, R_7, R_8 and R_9, is a phenyl group optionally substituted by one or more methoxy, ethoxy nor nitro groups. More preferably,

the aryl group is selected from: Ph, p-MeO-Ph, m-NO_2-Ph and p-NO_2-Ph.

If the compound of formula **III** is a dimer, the dimer bridge may be of the formula -O-$(CH_2)_p$-O-, where p is from 1 to 12, more preferably 3 to 9.

A fourth aspect of the present invention provides a compound with the formula **IV**:



(IV)

wherein:

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group (i.e. an alkyl group with one or more aryl substituents), preferably of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group, preferably of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group;

R_8' and R_8" are either independently selected from H, R or

together form a cyclic amine; and

n is from 1 to 7.

If R_8' and R_8" form a cyclic amine, then there is usually a single N atom in a ring which is otherwise carbocyclic and is preferably 5- or 6- membered and may be saturated or unsaturated. The ring may be fused to another ring system which may be aromatic, e.g. being a benzene ring. Thus for example the cyclic amine may be an indolyl or isoindolyl group. It is also possible that the cyclic amine contains one or more hetero atoms, in addition to N in the amine ring and/or in a fused ring and may also be substituted by one or more R groups.

If R is an aryl group, and contains a hetero atom, then R is a heterocyclic group. If R is an alkyl chain, and contains a hetero atom, the hetero atom may be located anywhere in the alkyl chain, e.g. $-O-C_2H_5$, $-CH_2-S-CH_3$, or may form part of or be a functional group e.g. carbonyl, hydroxy.

R is preferably selected from a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group, preferably of up to 12 carbon atoms, or an aryl group, preferably of up to 12 carbon atoms, optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is more preferred that R is selected from a lower alkyl group having 1 to 10 carbon atoms optionally substituted by one or more halo, hydroxy, amino, or nitro groups. It is particularly preferred that R is an unsubstituted straight or branched chain alkyl, having 1 to 10, preferably 1 to 6, and

more preferably 1 to 4, carbon atoms, e.g. methyl, ethyl, n-propyl, n-butyl or t-butyl.

R_7 is preferably an electron donating group, and is more preferably of the formula OR; particularly preferred are the groups OMe, OEt, and OBn. The term 'electron donating group' means a moiety covalently attached to a compound which is capable of increasing electron density in other parts of the compound.

In addition R_6 and R_9 are more preferably selected from H and OR; particularly preferred are OMe, OEt and OBn.

Alternatively, R_6, R_7 and R_9 may preferably be independently selected from R groups with the following structural characteristics:

(i) an optionally substituted phenyl group;

(ii) an optionally substituted ethenyl group;

(iii) an ethenyl group conjugated to an electron sink.

n is preferably 1 to 3, and more preferably 1.

A fifth aspect of the present invention is the use of a compound as described in the first, second, third or fourth aspects of the invention in a method of therapy. Conditions which may be treated include gene-based diseases, including, for example, neoplastic diseases and Alzheimer's Disease, and bacterial, parasitic and viral infections. In accordance with this aspect of the present invention, the compounds provided may be

administered to individuals. Administration is preferably in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors.

A compound may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

Pharmaceutical compositions according to the present invention, and for use in accordance with the present invention, may comprise, in addition to the active ingredient, i.e. a compound of formula **Ia**, **Ib**, **II**, **III** or **IV**, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous, or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum,

animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such a gelatin.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

A sixth aspect of the present invention is a pharmaceutical composition containing a compound of any one of formulae **Ia, Ib, II, III**, or **IV** as described above, and a pharmaceutically acceptable carrier or diluent. The preparation of pharmaceutical compositions is described in relation to the fifth aspect of the invention above.

A seventh aspect of the present invention provides the use of a compound of any one of formulae **Ia, Ib, II, III**, or **IV** as described above to prepare a medicament for the treatment of a gene-based disease, preferably a proliferative disease. The compound of formula **Ia, Ib, II, III**, or **IV** may be provided

together with a pharmaceutically acceptable carrier or diluent. The compounds may be used for the selective killing of oxic and hypoxic tumour cells in methods for the treatment of cancers, for example leukemias and particularly solid cancers including colon, CNS, renal, and lung tumours, including small cell lung carcinoma, and melanomas. In particular, dimers of formula **II** may be used for the selective killing of lung, colon, and CNS tumours and melanomas. The compounds of formula **III** and **IV** may be used selectively against melanomas.

A further aspect of the present invention provides the use of a compound of any one of formulae **Ia**, **Ib**, **II**, **III**, or **IV** as described above to prepare a medicament for the treatment of a viral, parasitic or bacterial infection. The preparation of a medicament is described in relation to the fifth aspect of the invention above.

In further aspects, the invention provides processes for preparing compounds according to the first, second, third and fourth aspects of the present invention.

Aspects of the invention will now be further described with reference to the accompanying drawings in which:
Figures 1 to 5 are synthesis routes for compounds of formula **Ia** of the present invention;
Figures 6 to 10 are synthesis routes for compounds of formula **II** of the present invention;
Figures 11 to 20 are synthesis routes for compounds of formula

III of the present invention;

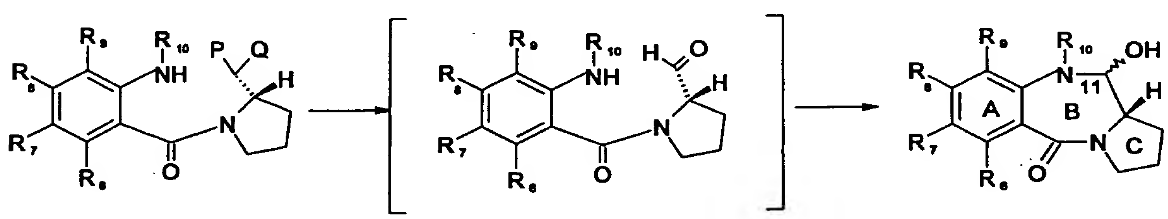
Figure 21 is a synthesis of an intermediate in the preparation of compounds of formula **IV** of the present invention;

Figure 22 is a synthesis routes for compounds of formula **IV** of the present invention; and

Figures 23 to 26 are graphs illustrating the cytotoxicity results of examples 5 to 8 respectively.

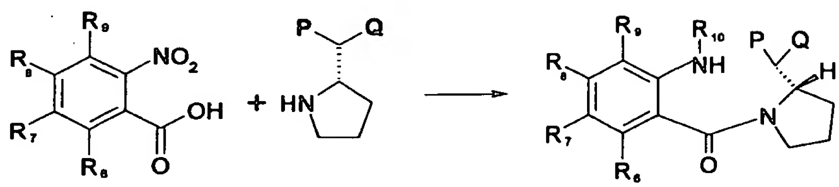
Preferred General Synthetic Strategies

A key step in a preferred route to compounds of formula **Ia**, **Ib**, **II**, **III** or **IV** is a cyclisation to produce the B-ring, involving generation of an aldehyde (or functional equivalent thereof) at what will be the 11-position, and attack thereon by the Pro-N10-nitrogen:



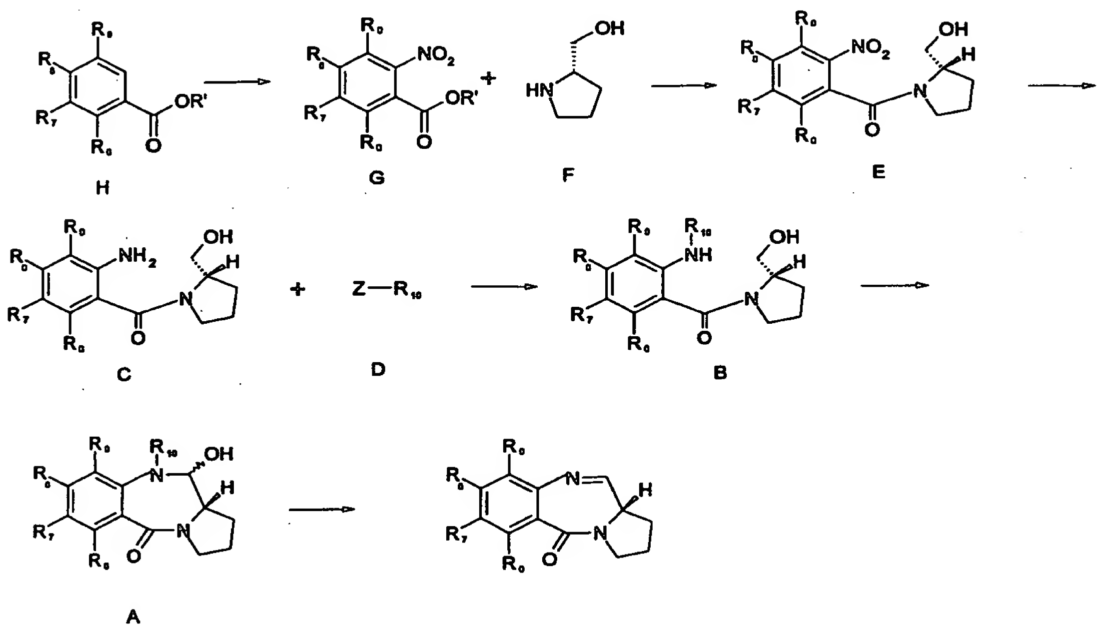
In this structure, no C-ring substitution or unsaturation is shown. R_8 represents $O(CH_2)_nCH_2COR'_8$ in compounds of formula **IV**. R_{10} is a nitrogen protecting group, preferably with a carbamate functionality bonded to the nitrogen of the PBD. The "masked aldehyde" -CPQ may be an acetal or thioacetal, in which case the cyclisation involves unmasking. Alternatively, it may be an alcohol -CHOH, in which case the reaction involves oxidation, e.g. by means of TPAP or DMSO (Swern oxidation).

The masked aldehyde compound can be produced by condensing a corresponding 2-substituted pyrrolidine with a 2-nitrobenzoic acid:



The nitro group can then be reduced to $-NH_2$ and protected by reaction with a suitable agent, e.g. a chloroformate, which provides the removable nitrogen protecting group in the compound of formula **I**.

A process involving the oxidation-cyclization procedure is illustrated in scheme 1 (an alternative type of cyclisation will be described later with reference to scheme 2).



Scheme 1

The imine/carbinolamine bond in the PBD (**A**) can be unprotected by standard methods to yield the desired compound, e.g. if R_{10} is Alloc, then the deprotection is carried using palladium to remove the N10 protecting group, followed by the elimination of water.

Exposure of the alcohol (**B**) (in which the Pro-N10-nitrogen is generally protected as carbamate) to tetrapropylammonium perruthenate (TPAP)/N-methylmorpholine N-oxide (NMO) over A4 sieves results in oxidation accompanied by spontaneous B-ring closure to afford the desired product. The TPAP/NMO oxidation procedure is found to be particularly convenient for small scale reactions while the use of DMSO-based oxidation methods, particularly Swern oxidation, proves superior for larger scale work (e.g. > 1 g).

The uncyclized alcohol (**B**) may be prepared by the reaction of a nitrogen protection reagent of formula **D**, which is preferably a chloroformate or acid chloride, to a solution of the amino alcohol **C**, generally in solution, generally in the presence of a base such as pyridine (preferably 2 equivalents) at a moderate temperature (e.g. at 0°C). Under these conditions little or no O-acylation is usually observed.

The key amino alcohol **C** may be prepared by reduction of the corresponding nitro compound **E**, by choosing a method which will leave the rest of the molecule intact. Treatment of **E** with tin (II) chloride in a suitable solvent, e.g. refluxing methanol, generally affords, after the removal of the tin salts, the

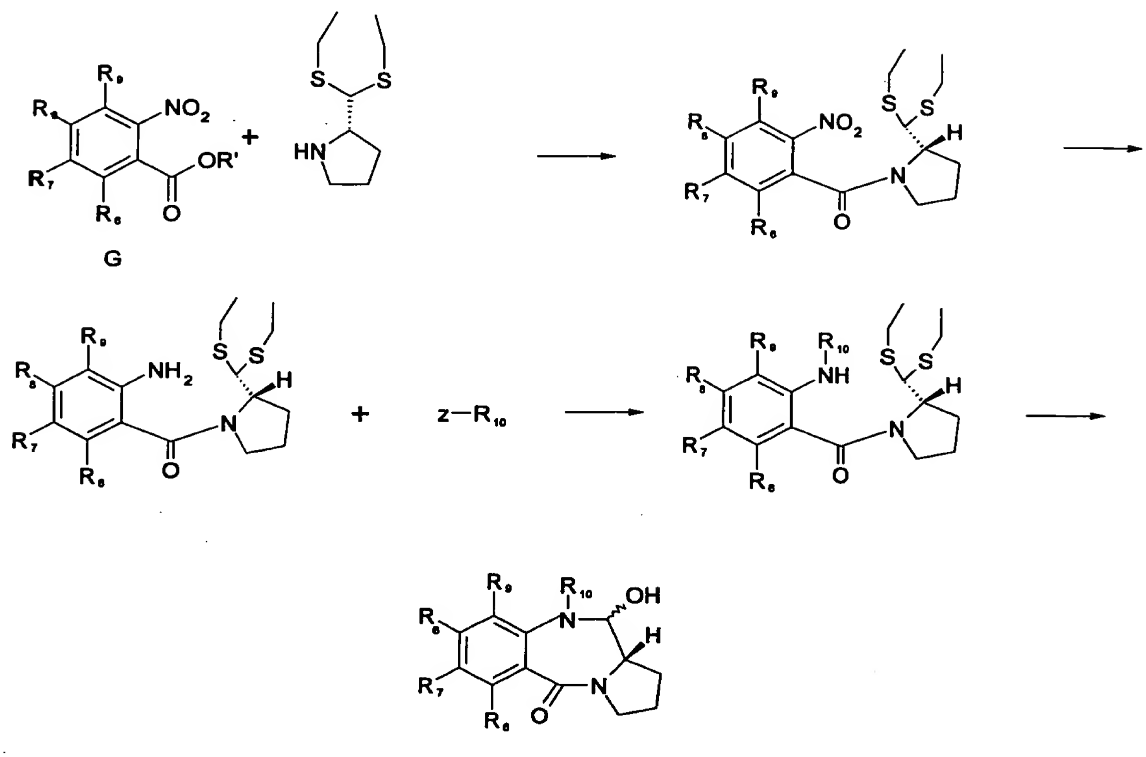
desired product in high yield.

Exposure of **E** to hydrazine/Raney nickel avoids the production of tin salts and may result in a higher yield of **C**, although this method is less compatible with the range of possible C and A-ring substituents. For instance, if there is C-ring unsaturation (either in the ring itself, or in R_2 or R_3), this technique may be unsuitable.

The nitro compound of formula **E** may be prepared by coupling the appropriate *o*-nitrobenzoyl chloride to a compound of formula **F**, e.g. in the presence of K_2CO_3 at -25°C under a N_2 atmosphere. Compounds of formula **F** can be readily prepared, for example by olefination of the ketone derived from L-trans-hydroxy proline. The ketone intermediate can also be exploited by conversion to the enol triflate for use in palladium mediated coupling reactions.

The *o*-nitrobenzoyl chloride is synthesised from the o-nitrobenzoic acid (or alkyl ester after hydrolysis) of formula **G**, which itself is prepared from the vanillic acid (or alkyl ester) derivative **H**. Many of these are commercially available and some are disclosed in Althuis, T.H. and Hess, H.J., J. Medicinal Chem., 20(1), 146-266.

Alternative Cyclisation (Scheme 2)



A

Scheme 2

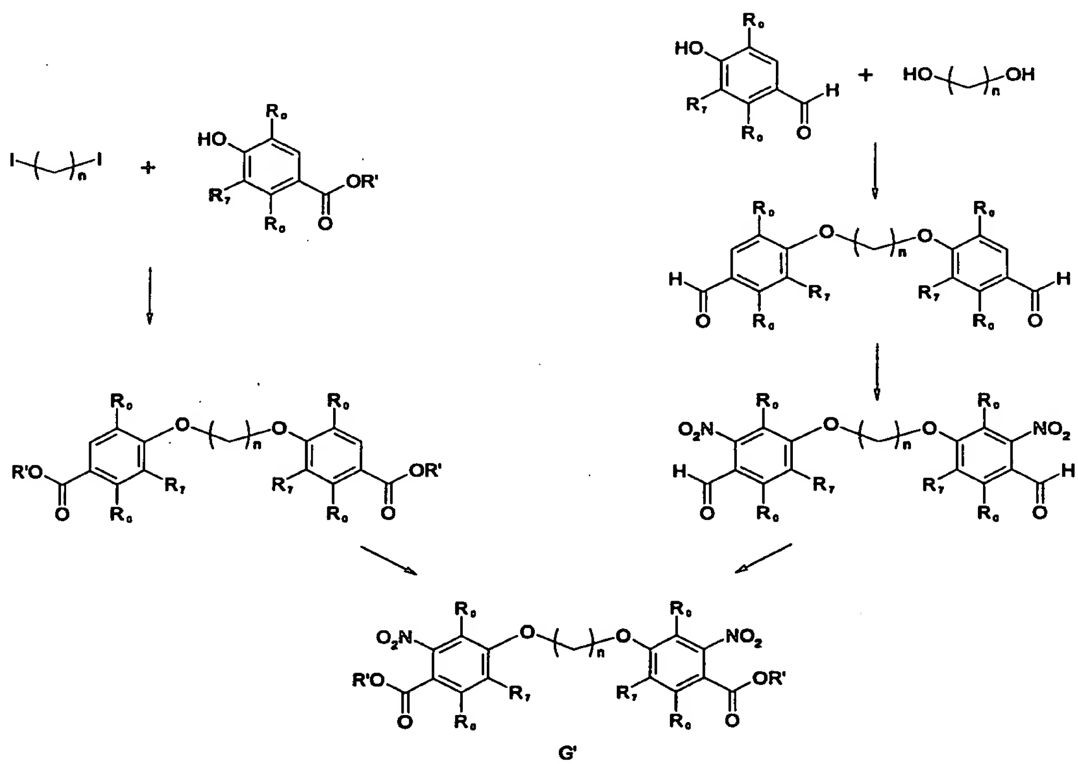
In scheme 1, the final or penultimate step was an oxidative cyclisation. An alternative, using thioacetal coupling, is shown in scheme 2. Mercury-mediated unmasking causes cyclisation to the protected PBD compound (**A**).

The thioacetal compound may be prepared as shown in scheme 2: the thioacetal protected C-ring [prepared via a literature method: Langley, D.R. & Thurston, D.E., *J. Organic Chemistry*, **52**, 91-97 (1987)] is coupled to the o-nitrobenzoic acid (or alkyl ester after hydrolysis) (**G**) using a literature procedure. The

resulting nitro compound cannot be reduced by hydrogenation, because of the thioacetal group, so the tin(II) chloride method is used to afford the amine. This is then N-protected, e.g., by reaction with a chloroformate or acid chloride, such as 2,2,2-trichloroethylchloroformate.

Acetal-containing C-rings can be used as an alternative in this type of route with deprotection involving other methods, including the use of acidic conditions.

Dimer Synthesis (Scheme 3)



Scheme 3

PBD dimers may be synthesized using the strategy developed for

the synthesis of the protected PBD monomers. The sysnthesis routes illustrated in scheme 3 show compounds when the dimer linkage is of the formula $-O-(CH_2)_n-O-$. The step of dimer formation is normally carried out to form a bis(nitro acid) **G'**. This compound can then be treated as compound **G** in either scheme 1 or scheme 2 above.

The bis(nitro acid) **G'** may be obtained by nitrating (e.g. using 70% nitric acid) the bis(carboxylic acid). This can be synthesised by alkylation of two equivalents of the relevant benzoic acid with the appropriate diiodoalkane under basic conditions. Many benzoic acids are commercially available and others can be synthesised by conventional methods. Alternatively, the relevant benzoic acid esters can be joined together by a Mitsunolo etherification with an appropriate alkanediol, followed by nitration, and then hydrolysis (not illustrated).

An alternative synthesis of the bis(nitro acid) involves oxidation of the bis(nitro aldehyde), e.g. with potassium permanganate. This can be obtained in turn by direct nitration of the bis(aldehyde), e.g. with 70% HNO_3. Finally, the bis(aldehyde) can be obtained via the Mitsunobu etherification of two equivalents of the benzoic aldehyde with the appropriate alkanediol.

Preferred Synthetic Strategies for Compounds of formula Ia

The synthesis route of scheme 1 is generally applicable to

compounds of formula **Ia**.

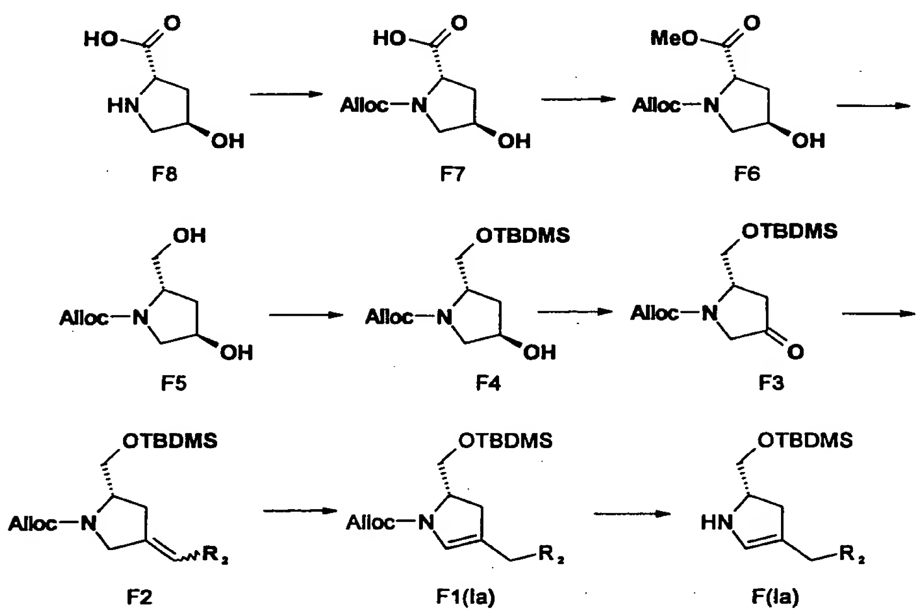
C2/C3-endo-unsaturated PBDs of formula **Ia** may be synthesised from their N10-carbamate protected precursors. Typically, palladium catalysed removal of an allyl carbamate may be used to generate the N10-C11 imine without affecting the key C2-unsaturation. For example, if the N10-C11 imine/carbinolamine is protected by an Alloc group, the C2/C3-endo-unsaturation is maintained during the Alloc cleavage reaction.

The reduction of the nitro-compound **E** as shown in scheme 1 with tin (II) chloride in refluxing methanol leaves the C2/C3-unsaturation unaffected. The hydrazine/Raney nickel method would not be suitable due to the double bond.

The compound of formula **F** may be used in its TBDMS protected form, and therefore a deprotection step has to be included to produce the amino-alcohol compound **E**.

The TBDMS ether, which is the product of the coupling of TBDMS protected compound with the appropriate o-nitrobenzoyl cloride, can be treated with AcOH:THF:H_2O (3:1:1). TBAF was found to be unsuitable for this transformation due to the rapid degradation of reaction products.

A class of requisite C-ring providing compounds **F** can be obtained



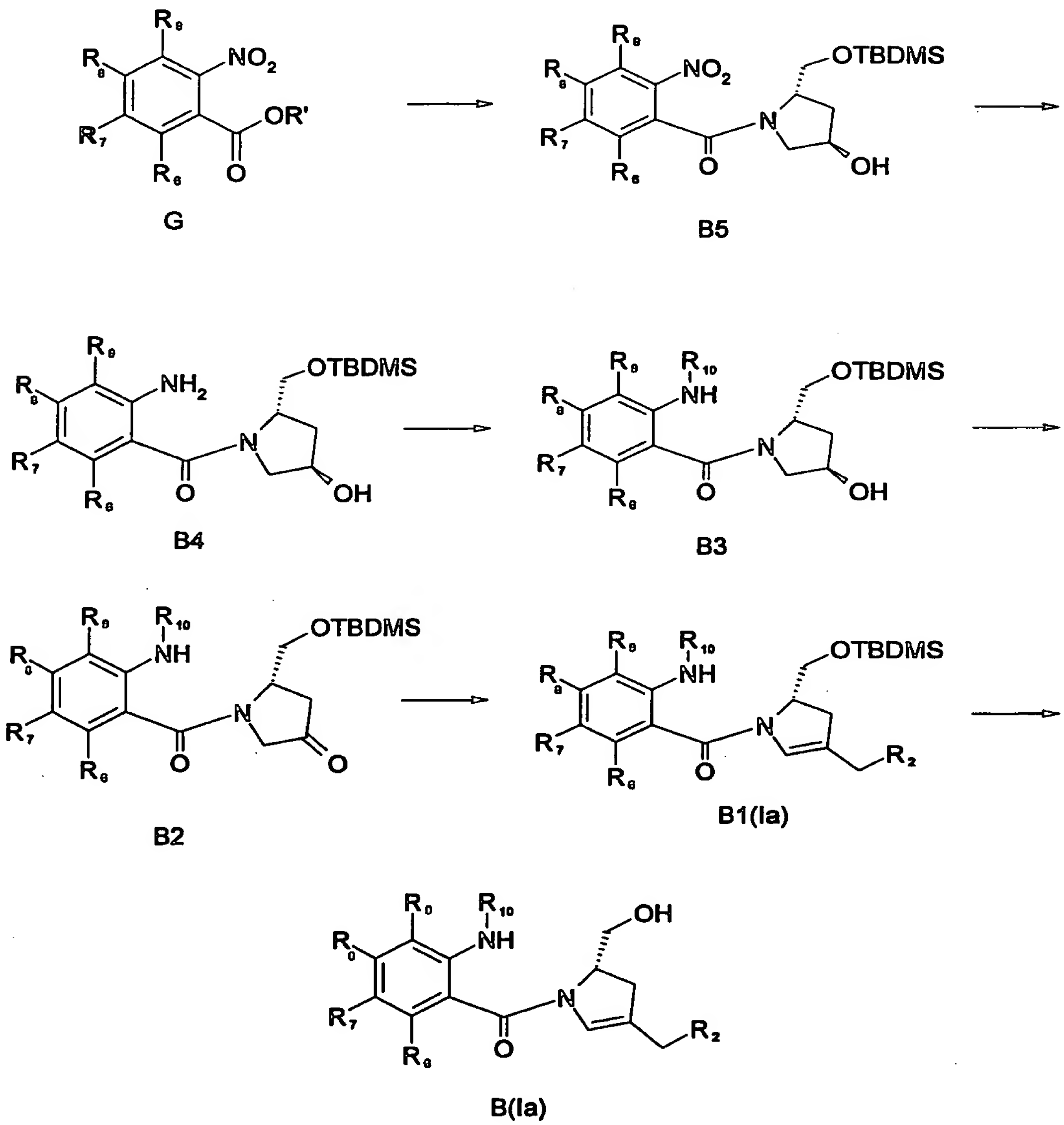
as shown in scheme 4.

Commercially available *trans*-4-hydroxy-L-proline **F8** can be N-alloc protected to give the allyl carbamate **F7** which can then be esterified using standard conditions. Hydride reduction of the ester **F6** furnishes the diol **F5**. Selective TBDMS protection of the diol gives a silyl ether **F4**, which can then be oxidised, using either Swern or TPAP oxidation, to provide the ketone **F3**.

The ketone **F3** can then undergo a Wittig reaction to yield a mixture of the E/Z *exo*-esters **F2** which can then be converted to the C2/C3-endo compound **F1(Ia)** upon treatment with excess sodium hydride. Palladium-mediated cleavage of the N-alloc protecting group (Dangles O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A.; *J. Org. Chem.* **1987**, *52*, 4984) yields the compound **F(Ia)**.

Alternative route to compounds of formula **Ia**

A more linear synthetic route to compound **B** of scheme 1 has been developed which enables larger scale production of the C2/C3-endo-unsaturated PBDs, and is shown in scheme 5.

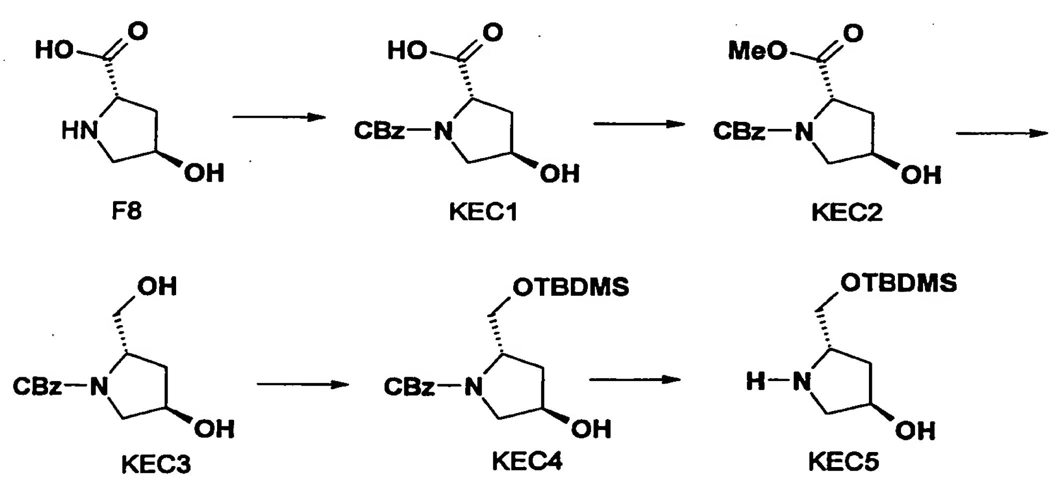


Scheme 5

The silyl protecting group may be cleaved in good yield by

treating **B1(Ia)** with AcOH:THF:H_2O (3:1:1). The key C2/C3-endo-unsaturation present in **B1(Ia)** may be introduced directly by performing the Horner-Emmons reaction on a ketone of type **B2**. Unlike the previous route (**Scheme 4**), the addition of extra NaH to ensure double-bond migration was not necessary for this substrate. Swern oxidation of the secondary alcohol **B3** may be used to furnish the ketone **B2**. The carbamate protected aniline **B3** may be prepared from the nitro compound **B5** in two steps. Firstly, the nitro group may be reduced to the aniline by employing the Raney nickel/hydrazine method because a compound of type **B5** lacks C2-unsaturation. This method is more advantageous than the tin (II) chloride procedure since the product is easier to isolate. The aniline **B4** may then be N-carbamate protected in high yield without significant carbonate formation at C2.

An amide of type **B5** may be synthesised by coupling an acid chloride of type **G** to the key amine **KEC5** (**Scheme 6**).



Scheme 6

Overall, this route has several advantages over the previous route which results in the larger scale production of the C2/C3-endo-unsaturated PBDs. Firstly, catalytic hydrogenation of **KEC4** allows large scale preparation of key intermediate **KEC5**. Secondly, the nitro reduction step may be carried out on an intermediate devoid of C2-unsaturation. Importantly, the double-bond migration observed during the Horner-Emmons reaction is spontaneous, so excess sodium hydride is not necessary. This double-bond migration has also been observed by other workers (Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641).

Parr-hydrogenation of **KEC4**, in order to cleave the Cbz protecting group, allowed the large scale synthesis of the key amino intermediate **KEC5**. The TBDMS ether **KEC4** was prepared in an analogous fashion to the corresponding Alloc protected intermediate **F4** (**Scheme 4**). Selective silylation of the primary alcohol **KEC3** was achieved using DBU as a silyl transfer agent. The diol **KEC3** was obtained from hydride reduction of ester **KEC2** which in turn was synthesised from carboxylic acid **KEC1**. N-Cbz protection of *trans*-4-hydroxy-L-proline (**F4**) was achieved by adopting a procedure reported in the literature (Bridges, R. J.; Stanley, M. S.; Anderson, M. W.; Cotman, C. W.; Chamberlain, R. A. *J. Med. Chem.* **1991**, *34*, 717).

Certain R_2 groups may require protection during the synthesis routes set out above, e.g. alcohols can be protected by using an acetate protecting group (see example 1(d))

The alternative synthesis routes are equally applicable to the synthesis of dimers.

Preferred Synthesis Strategies for Compounds of formula II

The synthesis route of scheme 1 is generally applicable to compounds of formula **II**.

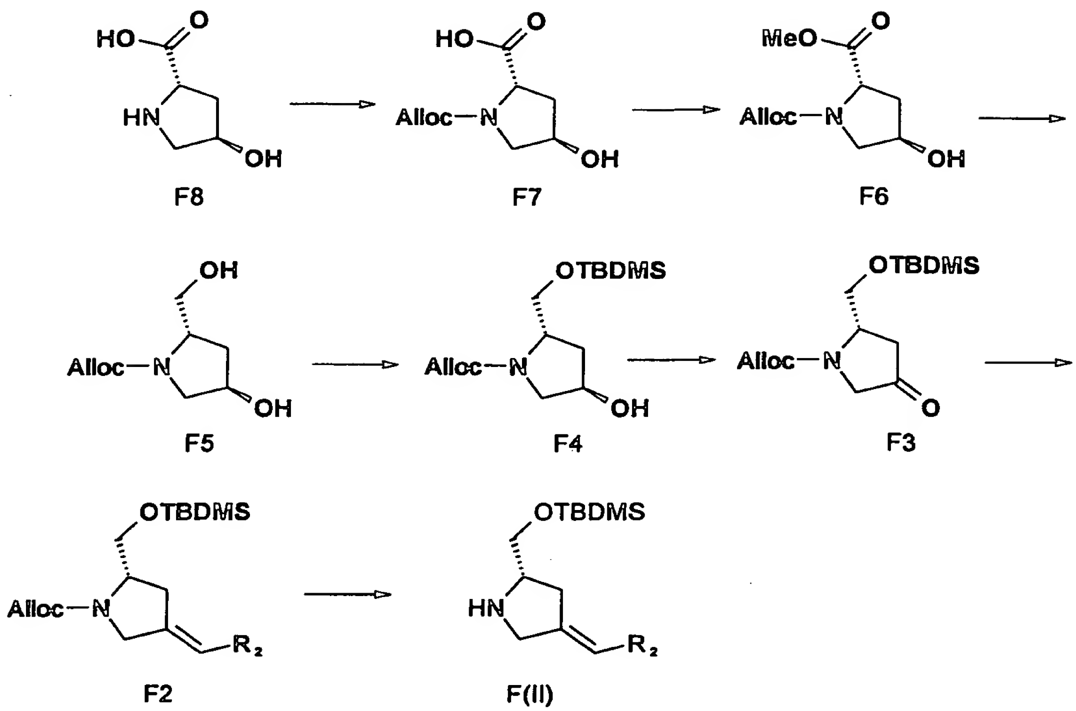
C2-unsaturated PBDs of formula **II** may be synthesised from their N10-carbamate protected precursors. Typically, palladium catalysed removal of an allyl carbamate may be used to generate the N10-C11 imine without affecting the key C2-unsaturation. Alternatively, cadmium-lead couple may be employed to cleave an N10-2,2,2-trichloroethyl carbamate from the protected PBD.

The reduction of the nitro-compound **E** as shown in scheme 1 with tin (II) chloride maintains the C2-unsaturation, although isolating the aniline **C** from the tin salts can be problematic.

The compound of formula **F** may be used in its TBDMS protected form, and therefore a deprotection step has to be included to produce the amino-alcohol compound **E**.

The TBDMS ether of type E, which is the product of the coupling of the TBDMS protected compound with the appropriate o-nitrobenzoyl chloride, can be treated with AcOH:THF:H_2O (3:1:1). TBAF was found to be unsuitable for this transformation due to the rapid degradation of reaction products.

C-ring providing compounds **F(II)** can be obtained as shown in scheme 7.



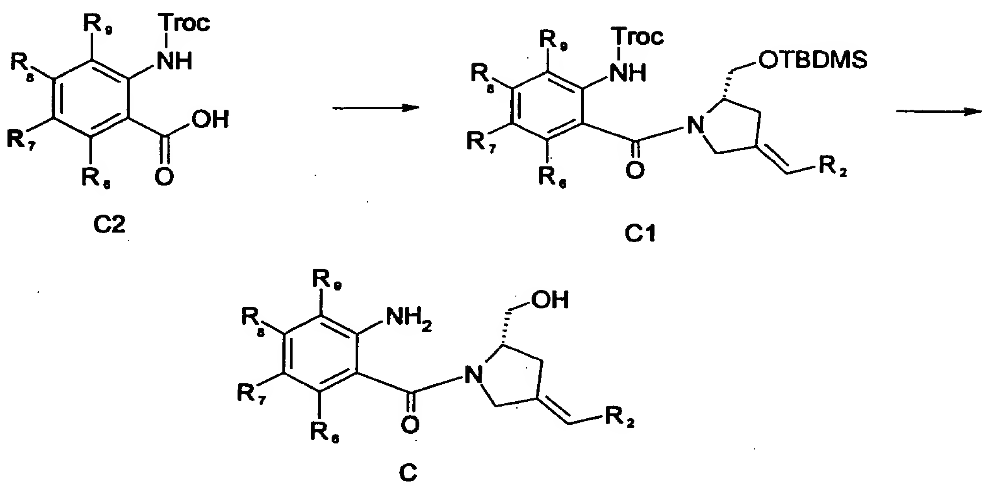
Scheme 7

Commercially available *trans*-4-hydroxy-L-proline **F8** can be N-alloc protected to give the allyl carbamate **F7** which can then be esterified using standard conditions. Hydride reduction of the ester **F6** furnishes the diol **F5**. Selective TBDMS protection of the diol gives a silyl ether **F4**, which can then be oxidised, using either Swern or TPAP oxidation, to provide the ketone **F3**.

The C2-olefinic functionality present in **F2** may be introduced by performing the Wittig reaction on ketone **F3**. Palladium-mediated

cleavage of the N-alloc protecting group (Dangles O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A.; *J. Org. Chem.* **1987**, *52*, 4984) yields compound **F(II)**.

<u>Alternative route to compound **C**</u>

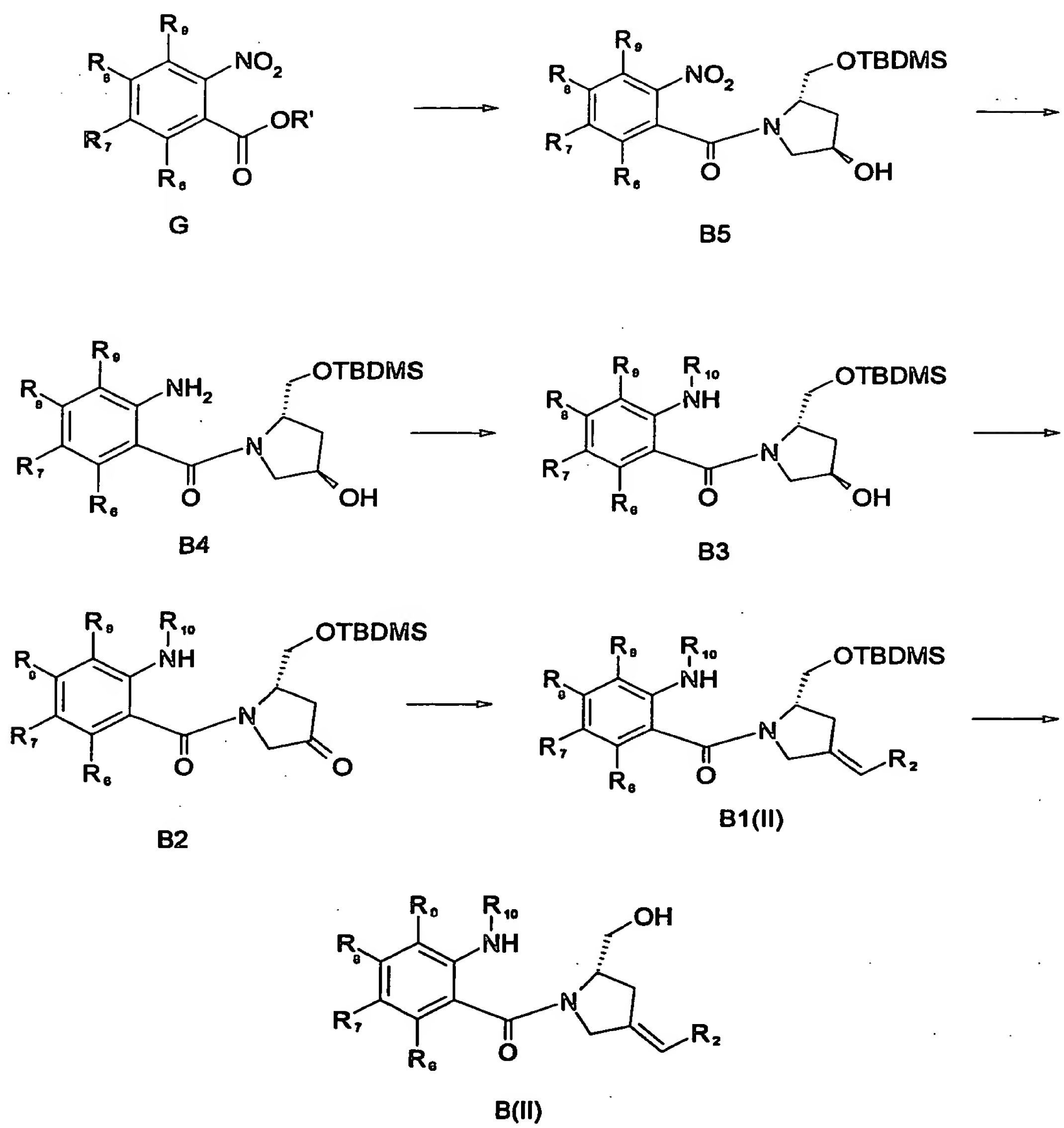


C2 C1 C

Scheme 8

An alternative route to compound C has been developed (**Scheme 8**). The amide of formula **C1** may be synthesised by forming the acid chloride of an N-Troc protected anthranilic acid of type **C2**. Interestingly, N-Troc anthranilic acids do not generate isatoic anhydrides, thus enabling amide formation reactions with amines of type **F(II)**. Simultaneous TBAF-mediated cleavage of the 2,2,2-trichloroethyl carbamate and TBDMS groups from **C1** may provide the key amino-alcohol **C**.

Alternative Route to compounds of formula **II**



Scheme 9

A more linear synthetic route to compound **B** of scheme 1 has been developed which enables larger scale production of the C2-unsaturated PBDs, and is shown in scheme 9. TBAF-mediated cleavage of the TBDMS group may be used to produce **B(II)** from

B1(II). The key C2-unsaturation present in **B1(II)** may be introduced by performing the Wittig olefination reaction on a ketone of type **B2**. Swern oxidation of the secondary alcohol **B3** may be used to furnish the ketone **B2**. The carbamate protected aniline **B3** may be prepared from the nitro compound **B5** in two steps. Firstly, the nitro group may be reduced to the aniline by employing the Raney nickel/hydrazine method because a compound of type **B5** lacks C2-unsaturation. This method is more advantageous than the tin (II) chloride procedure since the product is easier to isolate. The aniline **B4** may then be N-carbamate protected in high yield without significant carbonate formation at C2.

An amide of type **B5** may be synthesised by coupling an acid chloride of type **G** to the key amine **KEC5** (see scheme 6). Overall, this route has several advantages over the convergent route which allow larger scale production of the C2-unsaturated PBDs. Firstly, catalytic hydrogenation of **KEC4** allows large scale preparation of key intermediate **KEC5**. Secondly, the nitro reduction step may be carried out on an intermediate devoid of C2-unsaturation. Finally, the Wittig olefination may be performed in the latter stages of the synthetic route where large scale limitations are tolerated.

In dimer synthesis, the routes set out above may be used in preference to those set out in the overall synthetic strategies. In particular, the nitrogen-protecting group may advantageously be a carbamate, as protecting groups of this type may be removed in the final step by a variety of methods which, in general, do

not affect the key C2-unsaturation.

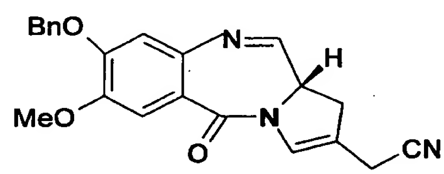
General Experimental Methods

Melting points (mp) were determined on a Gallenkamp P1384 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer 297 spectrophotometer. ^{1}H- and ^{13}C- NMR spectra were recorded on a Jeol GSX 270 MHZ FT-NMR spectrometer operating at 20°C +/-1°C. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS). Spin multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentuplet) or m (multiplet). Mass spectra (MS) were recorded using a Jeol JMS-DX 303 GC Mass Spectrometer (EI mode: 70eV, source 117-147°C). Accurate molecular masses (HRMS) were determined by peak matching using perfluorokerosene (PFK) as an internal mass marker, and FAB mass spectra were obtained from a glycerol/thioglycerol/trifluoroacetic acid (1:1:0.1) matrix with a source temperature of 180°C. Optical rotations at the Na-D line were obtained at ambient temperature using a Perkin-Elmer 141 Polarimeter. Analytical results were generally within +/-0.2% of the theoretical values. Flash chromatography was performed using Aldrich flash chromatography "Silica Gel-60" (E. Merck, 230-400 mesh). Thin-layer chromatography (TLC) was performed using GF_{254} silica gel (with fluorescent indicator) on glass plates. All solvents and reagents, unless otherwise stated, were supplied by the Aldrich Chemical Company Ltd. and were used as supplied without further purification. Anhydrous

solvents were prepared by distillation under a dry nitrogen atmosphere in the presence of an appropriate drying agent, and were stored over 4Å molecular sieves or sodium wire. Petroleum ether refers to the fraction boiling at 40-60°C.

Examples

Example 1(a): Synthesis of the 2-Cyanomethyl PBD (10, SB-A67) (see Figure 1)



Synthesis of the Nitro Alcohol (3)

A solution of the acid **1** (3.03 g, 10 mmol, 1 equiv) in freshly distilled CH_2Cl_2 (50 mL) was treated with oxalyl chloride (1.05 mL, 12 mmol, 1.2 equiv) under a nitrogen atmosphere and stirred. DMF (0.1 mL) was added and the solution effervesced. The reaction was allowed to stir overnight at RT. The following day the acid chloride solution was added dropwise over 2 h to a stirred mixture of the amine **2** (2.31 g, 10 mmol, 1 equiv) and TEA (3.48 mL, 25 mmol, 2.5 equiv) in freshly distilled CH_2Cl_2 (30 mL) while the temperature was kept under 0°C, under a nitrogen atmosphere. The reaction mixture was then allowed to warm to RT and stirred overnight. The solution was washed with $NaHCO_3$ (100 mL), saturated NH_4Cl (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil which was purified by flash chromatography (SiO_2, EtOAc) and provided the coupled compound **3** (3.24 g, 6.28 mmol, 62.8%) as a

yellow glass: ^1H NMR ($CDCl_3$, 270 MHz) rotamers: δ -0.10 (s, 6H, $Si(CH_3)_2$), 0.80 (s, 9H, $SiC(CH_3)_3$, 2.04-2.55 (m, 3H, 1-H, OH), 3.05-4.60 (m, 9H, 11-H, 11a-H, OMe, 3-H, 2-H), 5.20 (br s, 2H, OBn), 6.78 and 6.85 (2xs, 1H, 6-H), 7.27-7.47 (m, 5H, Ph), 7.73 and 7.76 (2xs, 1H, 9-H); ^{13}C NMR ($CDCl_3$, 270 MHz): δ -5.5, -5.4, 18.2, 25.7, 25.8, 36.3, 56.6, 57.2, 62.6, 70.2, 71.3, 109.0, 109.4, 127.6-128.8, 135.2, 137.3, 147.9, 154.7, 166.6; IR (neat): 3401, 3065, 3033, 2951, 2856, 2739, 2628, 1956, 1743, 1620, 1578, 1522, 1462, 1434, 1378, 1336, 1277, 1221, 1075, 1051, 1002, 914, 836, 779, 752, 697, 669, 650, 615; EIMS *m/z* (relative intensity) 516 ($M^{+\cdot}$, 0.6), 460 (29.8), 459 (92.6), 368 (7.9), 286 (49.6), 91 (100.0), 73 (9.5); FAB *m/z* (relative intensity) 517 ($M^{+\cdot}$ +1, 15.1), 385 (9.2), 286 (19.3), 92 (9.3), 91 (100.0), 75 (14.0), 73 (42.2).

Reduction to the Amino Alcohol (4)

A solution of hydrazine (3.11 mL, 100 mmol, 5 equiv) in MeOH (50 mL) was added dropwise to a refluxing solution of the nitro compound **3** (10.32 g, 20 mmol, 1 equiv), antibumping granules and Raney Ni (3.5 g) in MeOH (150 mL). After 1 h at reflux TLC (SiO_2, 5% MeOH-$CHCl_3$) revealed total consumption of starting material. The mixture was then treated with sufficient Raney Ni to decompose any unreacted hydrazine. After cooling to RT the mixture was filtered through Celite and the filtrate evaporated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (300 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide **4** (6.80 g, 14 mmol, 70%) as a pink oil which was carried through to the next stage without purification: ^1H NMR ($CDCl_3$,

270 MHz) rotamers: δ -0.001 (s, 6H, $Si(CH_3)_2$), 0.88 (br s, 9H, $SiC(CH_3)_3$), 1.96-2.23 (m, 2H, 1-H), 3.44-4.48 (m, 12H, 11-H, 3-H, OMe, NH_2, OH, 2-H, 11a-H), 5.09 (br s, 2H, OBn), 6.25 and 6.27 (2xs, 1H, 6-H), 6.68 and 6.73 (2xs, 1H, 9-H), 7.26-7.42 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 270 MHz): δ -5.4, 18.2, 25.9, 35.7, 56.9, 57.2, 70.4, 70.7, 103.2, 112.9, 113.4, 127.2, 127.4, 127.9, 128.6, 128.6, 136.7, 141.6; IR (neat): 3356.80, 2930.13, 2857.36, 2247.82, 1622.19, 1514.60, 1463.60, 1408.95, 1261.43, 1176.55, 1118.48, 1003.88, 911.00, 836.61, 778.15, 733.59, 697.72, 646.32.

Synthesis of the Alloc Pro-N10-Protected C2-Alcohol (5)

A solution of allyl chloroformate (1.54 mL, 14.48 mmol, 1.05 equiv) in freshly distilled CH_2Cl_2 (30 mL) was added dropwise to a stirred mixture of the amine **4** (6.70 g, 13.79 mmol, 1 equiv), pyridine (2.45 mL, 30.34 mmol, 2.2 equiv) in freshly distilled CH_2Cl_2 (200 mL), at 0°C under a nitrogen atmosphere. The mixture was allowed to warm at RT and stirred overnight. The following day TLC (SiO_2, 5% MeOH-$CHCl_3$) revealed reaction completion. The mixture was washed with saturated $CuSO_4$ (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark yellow oil. Flash chromatography (SiO_2, 30% EtOAc-petroleum ether) afforded the pure Alloc-compound **5** (6.70 g, 11.75 mmol, 85.2%) as a yellow oil: ^1H NMR ($CDCl_3$, 270 MHz) rotamers: δ 0.03 and 0.04 (2xs, 6H, $Si(CH_3)_2$), 0.89 (br s, 9H, $SiC(CH_3)_3$), 1.99-2.40 (m, 2H, 1-H), 3.56 (br s, 4H, 11-H, 3-H), 3.79 (s, 3H, OMe), 4.05-4.20 (m, 1H, 11a-H), 4.38 (s, 1H, 2-H), 4.58-4.62 (m, 3H, OH, Alloc), 5.16-5.37 (m, 4H, OBn, Alloc), 5.86-6.00 (m, 1H, Alloc), 6.80 (s, 1H, 6-H), 7.30-7.48 (m, 5H,

Ph), 7.80 (s, 1H, 9-H), 8.86 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 270 MHz): δ -5.5, -5.4, 18.1, 25.8, 35.6, 56.4, 57.2, 60.4, 65.8, 70.5, 70.7, 106.4, 111.7, 116.4, 118.0, 127.7-128.6, 132.5, 136.3, 144.3, 150.2, 153.8, 169.4; IR (neat): 3336, 3067, 2953, 2931, 2858, 1732, 1600, 1525, 1464, 1408, 1327, 1225, 1175, 1121, 1048, 1028, 1002, 937, 837, 812, 778, 744, 698, 671, 636, 608, 562; EIMS *m/z* (relative intensity) 570 ($M^{+\cdot}$, 35.0), 513 (27.2), 340 (19.3), 149 (24.3), 91 (24.1), 77 (16.4), 58 (33.0), 57 (100.0), 44 (27.2), 39 (39.8); $[\alpha]^{23}_D = -55.94^\circ$ (c = 1.010, $CHCl_3$).

Oxidation to the C2-Ketone (6)

A solution of DMSO (2.50 mL, 35.25 mmol, 3 equiv) in freshly distilled CH_2Cl_2 (200 mL) was added dropwise over 1.5 h to a stirred solution of oxalyl chloride (8.81 mL of a 2M solution in CH_2Cl_2, 17.62 mmol, 1.5 equiv) at -55/-60°C (liquid nitrogen/$CHCl_3$) under a nitrogen atmosphere. After 30 min stirring at -55°C, a solution of the secondary alcohol **5** (6.70 g, 11.75 mmol, 1 equiv) in CH_2Cl_2 (150 mL) was added dropwise to the reaction mixture over 1.5 h. Following stirring at -55/-60°C for 45 min the reaction was treated dropwise with a solution of TEA (11.14 mL, 79.90 mmol, 6.8 equiv) in CH_2Cl_2 (50 mL) over a period of 40 min. The mixture was stirred for a further 45 min at -30°C and was then allowed to warm to RT. The reaction was then treated with brine (150 mL), cooled to 0°C and acidified to pH=2 with concentrated HCl. The organic phase was washed with H_2O (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the ketone **6** as a dark orange oil (6.18 g, 10.88

mmol, 93%), sufficiently pure by TLC (SiO_2, 40% EtOAc-petroleum ether) to be carried through to the next stage without further purification: ^1H NMR ($CDCl_3$, 270 MHz) rotamers: δ 0.04 and 0.05 (2xs, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 2.47-2.78 (m, 2H, 1-H), 3.66-4.10 (m, 8H, 3-H, OMe, 11-H, 11a-H), 4.62-4.65 (m, 2H, Alloc), 4.80-5.40 (m, 4H, OBn, Alloc), 5.88-6.03 (m, 1H, Alloc), 6.76 (s, 1H, 6-H), 7.27-7.49 (m, 5H, Ph), 7.90 (s, 1H, 9-H), 8.62 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 270 MHz): δ -5.8, -5.7, 18.0, 25.6, 25.7, 56.5, 65.8, 68.0, 70.7, 106.4, 111.0, 118.2, 127.7-128.6, 132.4, 136.1, 150.6, 153.4, 208.9; IR (neat): 3510, 3332, 2957, 2870, 2740, 1959, 1771, 1738, 1633, 1537, 1428, 1274, 1233, 1120, 1029, 844, 785, 700; EIMS *m/z* (relative intensity) 568 ($M^{+\cdot}$, 90.6), 512 (28.7), 511 (79.8), 453 (12.1), 340 (38.6), 298 (12.7), 282 (16.9), 172 (23.9), 91 (100.0), 41 (15.1); $[\alpha]^{23}_D = -1.98^\circ$ (c = 1.010, $CHCl_3$).

Insertion of the C2-Cyanomethyl Group (7)

Sodium hydride (0.70 g of a 60% dispersion in mineral oil, 17.60 mmol, 2.5 equiv) was stirred in petroleum ether for 10 min. The suspension was allowed to settle and the solvent transferred under nitrogen from the flask via a double-tipped needle. The remaining residue was suspended in freshly distilled anhydrous THF (50 mL), cooled to 0°C and treated dropwise with a solution of the diethyl cyanomethylphosphonate (11.14 mL, 79.90 mmol, 6.8 equiv) in THF (60 mL) under a nitrogen atmosphere. The mixture was allowed to warm to RT and stir for 1.5 h. After cooling to 0°C the reaction mixture was treated dropwise with a solution of the ketone **6** (11.14 mL, 79.90 mmol, 6.8 equiv) in THF (40 mL).

After stirring overnight TLC (SiO_2, 30% EtOAc-petroleum ether) revealed almost complete consumption of starting material. THF was evaporated *in vacuo* and the resulting residue treated with a saturated solution of $NaHCO_3$ (100 mL) and EtOAc (100 mL). The aqueous layer was washed with EtOAc (100 mL) and the combined organic layers were then washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown glass which was subjected to flash chromatography (SiO_2, 30% EtOAc-petroleum ether) to provide the pure cyano compound **7** (2.6 g, 4.40 mmol, 63%) as a yellow glass: ^1H NMR ($CDCl_3$, 270 MHz): δ 0.03-0.09 (m, 6H, $Si(CH_3)_2$), 0.88 (m, 9H, $SiC(CH_3)_3$), 2.68-2.91 (m, 2H, 1-H), 3.12-3.13 (m, 2H, 12-H), 3.72-3.76 (m, 2H, 11-H), 3.82 (s, 3H, OMe), 4.62-4.65 (m, 2H, Alloc), 4.75 (m, 1H, 11a-H), 5.19 (s, 2H, OBn), 5.22-5.39 (m, 2H, Alloc), 5.88-6.02 (m, 1H, Alloc), 6.59 (s, 1H, 3-H), 6.68 (s, 1H, 6-H), 7.32-7.50 (m, 5H, Ph), 7.95 (s, 1H, 9-H), 8.72 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 270 MHz): δ -5.4, 17.5, 18.1, 25.6-25.7, 34.0, 56.6, 59.8, 62.3, 65.8, 70.7, 106.1, 111.8, 114.0, 116.2, 118.1, 127.7-129.3, 132.4, 132.8, 136.1, 144.2, 150.9, 153.4, 166.1; IR (neat): 3337, 3067, 3034, 2954, 2930, 2857, 2253, 1732, 1622, 1599, 1524, 1495, 1464, 1408, 1362, 1336, 1259, 1205, 1166, 1116, 1051, 1026, 992, 914, 839, 778, 735, 698, 647; EIMS *m/z* (relative intensity) 591 ($M^{+\cdot}$, 20.1), 534 (15.0), 340 (67.5), 282 (20.9), 252 (25.6), 195 (32.4), 91 (100.0); HRMS *m/z* Calcd for 591.2765 ($C_{32}H_{41}N_3O_6Si$). Found 591.2758; $[\alpha]^{23}_D$ = -83.25° (c = 1.015, $CHCl_3$).

Deprotected Alcohol (8)

Glacial AcOH (15 mL) was added to a stirred solution of the silyl ether **7** (2.10 g, 3.55 mmol) in THF (10 mL) and H_2O (15 mL). The reaction mixture was allowed to stir at RT and monitored every hour by TLC (SiO_2, 30% EtOAc-petroleum ether). Over the course of 3 h AcOH (10 mL) was added in two further portions. The mixture was stirred for a total of 4 h at which time the reaction had gone to completion. The mixture was then cooled to 0°C and treated dropwise with a 10% solution of $NaHCO_3$ in H_2O (50 mL). The aqueous solution was extracted with EtOAc (3x20 mL) and the combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil. Flash chromatography (SiO_2, 5% MeOH-$CHCl_3$) afforded the free alcohol **8** (1.40 g, 2.93 mmol, 83%) as a yellow glass: ^1H NMR ($CDCl_3$, 270 MHz): δ 2.41-3.02 (m, 2H, 1-H), 3.13 (s, 2H, 12-H), 3.70-4.10 (m, 6H, 11-H, OMe, OH), 4.61-4.64 (m, 2H, Alloc), 4.76 (m, 1H, 11a-H), 5.16 (s, 2H, OBn), 5.23-5.28 (m, 2H, Alloc), 5.87-6.02 (m, 1H, Alloc), 6.53 (s, 1H, 3-H), 6.78 (s, 1H, 6-H), 7.27-7.48 (m, 5H, Ph), 7.75 (s, 1H, 9-H), 8.45 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 270 MHz): δ 17.4, 34.8, 56.8, 61.5, 65.1, 65.9, 70.8, 106.9, 111.8, 114.4, 116.1, 118.2, 127.7-129.1, 132.1, 132.4, 136.0, 144.8, 151.1, 153.7, 167.3; IR (neat): 3340, 3067, 2934, 2856, 2252, 1732, 1601, 1523, 1455, 1407, 1374, 1336, 1226, 1167, 1111, 1048, 1028, 996, 938, 869, 838, 768, 745, 698, 668, 636, 608; EIMS *m/z* (relative intensity) 477 ($M^{+\cdot}$, 14.6), 340 (46.9), 282 (13.0), 91 (100.0); HRMS *m/z* Calcd for 477.1900 ($C_{26}H_{27}N_3O_6$. Found 477.1962; $[\alpha]^{23}{}_D = -67.42°$ (c = 1.068, $CHCl_3$).

N10-Protected Cyclized PBD (9)

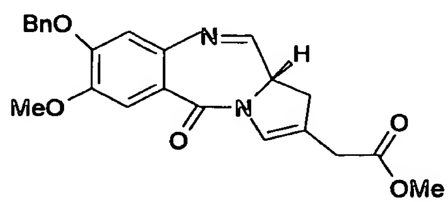
A solution of DMSO (0.75 mL, 10.55 mmol, 3.6 equiv) in freshly distilled CH_2Cl_2 (40 mL) was added dropwise at a rapid rate to a stirred solution of oxalyl chloride (2.64 mL of a 2M solution in CH_2Cl_2, 5.27 mmol, 1.8 equiv) at -40/-50°C (liquid nitrogen/chlorobenzene) under a nitrogen atmosphere. After 5 min stirring at -45°C, a solution of the primary alcohol **8** (1.40 g, 2.93 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was added dropwise to the reaction mixture over 45 min. Following stirring at -45°C for 45 min the reaction was treated dropwise with a solution of TEA (1.72 mL, 12.31 mmol, 4.2 equiv) in CH_2Cl_2 (20 mL) over a period of 30 min. The mixture was stirred for a further 40 min at -45°C and was then allowed to warm to RT and diluted with 20 mL CH_2Cl_2. The reaction was then cooled to 0°C and washed with 1N HCl (200 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow foam which was subjected to flash chromatography (SiO_2, 5% MeOH-$CHCl_3$) to provide the pure ring closed compound **9** (0.95 g, 2.00 mmol, 68%) as a slightly yellow glass: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 2.69-3.14 (m, 2H, 1-H), 3.24 (s, 2H, 12-H), 3.84-3.98 (m, 6H, 11-H, OMe, OH), 4.46 (m, 2H, Alloc), 5.07-5.18 (m, 4H, OBn, Alloc),5.60-5.80 (m, 2H, Alloc, 11a-H), 6.74 (s, 1H, 3-H), 7.04 (s, 1H, 6-H), 7.24-7.43 (m, 6H, Ph, 9-H); ^{13}C NMR ($CDCl_3$, 270MHz):δ 17.5, 36.5, 56.2, 59.6, 66.9, 71.1, 85.7, 111.0, 113.2, 114.7, 116.1, 118.3, 124.6, 127.3-128.7, 131.7, 136.0, 149.2, 150.6, 163.6; IR (neat): 3396, 3089, 2938, 2615, 2251, 1707, 1602, 1513, 1432, 1308, 1219, 1113, 1045, 918, 869, 790, 735, 698, 648; EIMS *m/z* (relative intensity) 475 ($M^{+\cdot}$, 34.2), 340 (25.4), 339 (35.0), 279 (10.3), 134 (10.6),

91 (100.0); HRMS *m/z* Calcd for 475.1743 ($C_{26}H_{25}N_3O_6$). Found 475.1883; $[\alpha]^{23}{}_D$ = +101.46° (c = 1.030, $CHCl_3$).

C2-Cyanomethyl PBD (10, SB-A67)

Triphenylphosphine (25 mg, 0.095 mmol, 0.05 equiv), pyrrolidine (167 µl, 2.0 mmol, 1.05 equiv) and $Pd(PPh_3)_4$ (56 mg, 0.048 mmol, 0.025 equiv) were added sequentially to a stirred solution of the Alloc-compound **9** (900 mg, 1.90 mmol, 1 equiv) in freshly distilled dry CH_2Cl_2 (100 mL). The reaction mixture was allowed to stir at RT under a nitrogen atmosphere for 2 h by which time TLC (SiO_2, 1% MeOH-$CHCl_3$) revealed reaction completion. The mixture was evaporated *in vacuo* and the residue applied to a gravity chromatography column (SiO_2, 1% MeOH-$CHCl_3$) to isolate the PBD **SB-A67** (720 mg, 1.93 mmol, 100%) as a yellow glass: ^1H NMR ($CDCl_3$, 270 MHz): 3.05-3.40 (m, 4H, 1-H, 12-H), 3.95 (s, 3H, OMe), 4.38 (m, 1H, 11a-H), 5.21 (s, 2H, OBn), 6.84 (s, 1H, 6-H), 7.06 (s, 1H, 3-H), 7.27-7.70 (m, 6H, Ph, 9-H), 7.80 (d, 1H, 11a-H, J = 3 Hz); ^{13}C NMR ($CDCl_3$, 270 MHz): δ 17.4, 36.8, 53.9, 56.3, 70.9, 111.7, 111.9, 112.8, 116.0, 118.7, 120.7, 127.1-128.7, 132.0, 136.0, 140.2, 148.3, 151.2, 161.8; IR (neat): 3353, 2931, 2251, 2222, 1604, 1508, 1437, 1247, 1120, 1000, 913, 874, 724, 697, 542; EIMS *m/z* (relative intensity) 373 ($M^{+\cdot}$, 9.8), 371 (24.4), 280 (12.5), 91 (100.0); HRMS *m/z* Calcd for 373.1426 ($C_{22}H_{19}N_3O_3$). Found 373.1364; $[\alpha]^{23}{}_D$ = 254.5° (c = 1.045, $CHCl_3$).

Example 1(b): Synthesis of the 2-Methoxycarbonylmethyl PBD (5, SJG-245) (see Figure 2)



(2*S*,4*R*)-*N*-(Allyloxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (12)

A solution of allyl chloroformate (29.2 mL, 33.2 g, 275 mmol) in THF (30 mL) was added dropwise to a suspension of *trans*-4-hydroxy-L-proline **(11)** (30 g, 229 mmol) in a mixture of THF (150 mL) and H_2O (150 mL) at 0°C (ice/acetone), whilst maintaining the pH at 9 with 4 N NaOH. After stirring at 0°C for 1 h at pH 9, the aqueous layer was saturated with NaCl, and the mixture diluted with EtOAc (100 mL). The aqueous layer was separated, washed with EtOAc (100 mL) and the pH adjusted to 2 with conc. HCl. The resulting milky emulsion was extracted with EtOAc (2 X 100 mL), washed with brine (200 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the allyl carbamate **12** as a clear viscous oil (42.6 g, 87%): $[\alpha]^{20}{}_D$ = −62.1 ° (*c* = 0.69, MeOH); ^1H NMR (270 MHz, $CDCl_3$ + DMSO-d_6) (Rotamers) δ 5.98-5.81 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.40-5.14 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.64-4.42 (m, 4H, $NCO_2CH_2CH{=}CH_2$, $NCH_2CHOHCH_2$ and $CHCO_2H$), 3.82-3.51 (m, 2H, $NCH_2CHOHCH_2$), 2.34-2.08 (m, 2H, $NCH_2CHOHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$ + DMSO) (Rotamers) δ 175.0 and 174.5 (CO_2H), 155.1 and 154.6 (NC=O), 132.9 and 132.8 ($NCO_2CH_2CH{=}CH_2$), 117.6 and 116.7 ($NCO_2CH_2CH{=}CH_2$), 69.5 and 68.8 (NCH_2CHOH), 65.9 and 65.8

($NCO_2CH_2CH{=}CH_2$), 58.0 and 57.7 ($CHCO_2H$), 55.0 and 54.5 (NCH_2CHOH), 39.3 and 38.3 ($NCH_2CHOHCH_2$); MS (EI), *m/z* (relative intensity) 215 ($M^{+\cdot}$, 10) 197(12), 170 ($M-CO_2H$, 100), 152 (24), 130 ($M-CO_2C_3H_5$, 97), 126 (34), 112 (50), 108 (58), 86 (11), 68 (86), 56 (19); IR (Neat) 3500-2100 (br, OH), 2950, 1745 and 1687 (br, C=O), 1435, 1415, 1346, 1262, 1207, 1174, 1133, 1082, 993, 771 cm^{-1}; exact mass calcd for $C_9H_{13}NO_5$ *m/e* 215.0794, obsd *m/e* 215.0791.

Methyl (2*S*,4*R*)-*N*-(Allyloxycarbonyl)-4-hydroxypyrrolidine-2-carboxylate (13)

A catalytic amount of concentrated H_2SO_4 (4.5 mL) was added to a solution of Alloc-hydroxyproline **(12)** (43 g, 200 mmol) in MeOH (300 mL) at 10°C (ice) and the reaction mixture was then heated at reflux for 2 h. After cooling to room temperature the reaction mixture was treated with TEA (43 mL) and the MeOH evaporated *in vacuo*. The residue was dissolved in EtOAc (300 mL), washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a viscous oil. Purification by flash chromatography (40% EtOAc/Petroleum Ether) removed the high R_f impurity to provide the pure ester **13** as a transparent yellow oil (19.6 g, 43%): $[\alpha]^{23}{}_D = -79.0$ ° (c = 0.35, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 5.98-5.78 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.35-5.16 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.65-4.45 (m, 4H, $NCO_2CH_2CH{=}CH_2$, $NCH_2CHOHCH_2$ and $NCHCO_2CH_3$), 3.75 and 3.72 (s x 2, 3H, OCH_3), 3.70-3.54 (m, 2H, $NCH_2CHOHCH_2$), 3.13 and 3.01 (br s x 2, 1H, OH), 2.39-2.03 (m, 2H, $NCH_2CHOHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 173.4 and 173.2 (CO_2CH_3), 155.0 and 154.6 (NC=O),

132.6 and 132.4 ($NCO_2CH_2\mathit{C}H=CH_2$), 117.6 and 117.3 ($NCO_2CH_2CH=\mathit{C}H_2$), 70.0 and 69.2 ($NCH_2\mathit{C}HOH$), 66.2 ($NCO_2\mathit{C}H_2CH=CH_2$), 57.9 and 57.7 ($N\mathit{C}HCO_2CH_3$), 55.2 and 54.6 ($N\mathit{C}H_2CHOH$), 52.4 ($O\mathit{C}H_3$), 39.1 and 38.4 ($NCH_2CHOH\mathit{C}H_2$); MS (EI), *m/z* (relative intensity) 229 ($M^{+\cdot}$, 7), 170 ($M-CO_2Me$, 100), 144 ($M-CO_2C_3H_5$, 12), 126 (26), 108 (20), 68 (7), 56 (8); IR (Neat) 3438 (br, OH), 2954, 1750 and 1694 (br, C=O), 1435, 1413, 1345, 1278, 1206, 1130, 1086, 994, 771 cm^{-1}; exact mass calcd for $C_{10}H_{15}NO_5$ *m/e* 229.0950, obsd *m/e* 229.0940.

(2*S*,4*R*)-*N*-(Allyloxycarbonyl)-4-hydroxy-2-(hydroxymethyl) pyrrolidine (14)

A solution of the ester **13** (19.5 g, 85 mmol) in THF (326 mL) was cooled to 0°C (ice/acetone) and treated with $LiBH_4$ (2.78 g, 128 mmol) in portions. The reaction mixture was allowed to warm to room temperature and stirred under a nitrogen atmosphere for 2.5 h at which time TLC (50% EtOAc/Petroleum Ether) revealed complete consumption of ester **13**. The mixture was cooled to 0°C and water (108 mL) was carefully added followed by 2 N HCl (54 mL). After evaporation of the THF *in vacuo*, the mixture was neutralised to pH 7 with 10 N NaOH and saturated with solid NaCl. The saturated aqueous solution was then extracted with EtOAc (5 X 100 mL), the combined organic layers washed with brine (200 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to furnish the pure diol **14** as a clear colourless oil (16.97 g, 99%): $[\alpha]^{24}_D = -57.0°$ (c = 0.61, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.01-5.87 (m, 1H, $NCO_2CH_2C\mathit{H}=CH_2$), 5.36-5.20 (m, 2H, $NCO_2CH_2CH=C\mathit{H}_2$), 4.84 (br s, 1H, $NCHC\mathit{H}_2OH$), 4.60 (d, 2H, J = 5.31 Hz, $NCO_2C\mathit{H}_2CH=CH_2$), 4.39 (br s, 1H, $NCHC\mathit{H}_2OH$), 4.18-4.08 (m, 1H, 3.35, $NCH_2C\mathit{H}OH$), 3.90-3.35 (m,

4H, NCH_2CHOH, $NCHCH_2OH$, and *OH*), 3.04 (br s, 1H, *OH*), 2.11-2.03 (m, 1H, $NCH_2CHOHCH_2$), 1.78-1.69 (m, 1H, $NCH_2CHOHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.1 (NC=O), 132.6 ($NCO_2CH_2CH=CH_2$), 117.7 ($NCO_2CH_2CH=CH_2$), 69.2 (NCH_2CHOH), 66.4 and 66.2 ($NCO_2CH_2CH=CH_2$ and $NCHCH_2OH$), 59.2 ($NCHCH_2OH$), 55.5 (NCH_2CHOH), 37.3 ($NCH_2CHOHCH_2$); MS (EI), *m/z* (relative intensity) 201 ($M^{+\cdot}$, 2), 170 ($M-CH_2OH$, 100), 144 ($M-OC_3H_5$, 6), 126 (26), 108 (20), 68 (9); IR (Neat) 3394 (br, OH), 2946, 2870, 1679 (C=O), 1413, 1339, 1194, 1126, 1054, 980, 772 cm^{-1}; exact mass calcd for $C_9H_{15}NO_4$ *m/e* 201.1001, obsd *m/e* 201.1028.

(2*S*,4*R*)-*N*-(Allyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (15)

A solution of the diol **14** (16.97 g, 84 mmol) in CH_2Cl_2 (235 mL) was treated with TEA (11.7 mL, 8.5 g, 84 mmol) and stirred for 15 min at room temperature. TBDMSCl (9.72 g, 64 mmol) and DBU (16.8 mmol, 2.51 mL, 2.56 g) were added and the reaction mixture stirred for a further 16 h under a nitrogen atmosphere. The reaction mixture was diluted with EtOAc (500 mL), washed with saturated NH_4Cl (160 mL), brine (160 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil which was a mixture of the required product (major component), unreacted diol and the presumed disilyated compound by TLC (50% EtOAc/Petroleum Ether). Flash chromatography (20-100% EtOAc/Petroleum Ether) isolated the 3 components, to provide the monosilylated compound **15** as a slightly yellow transparent oil (13.85 g, 52%): $[\alpha]^{21}_D = -58.6$ ° (*c* = 1.14, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 6.01-5.86 (m, 1H, $NCO_2CH_2CH=CH_2$), 5.34-5.18 (m, 2H, $NCO_2CH_2CH=CH_2$), 4.59-

4.49 (m, 3H, $NCO_2CH_2CH{=}CH_2$ and NC*H*CH_2OTBDMS), 4.06-3.50 (m, 5H, NCH_2CHOH, NCH_2C*H*OH and $NCHCH_2$OTBDMS), 2.20-2.01 (m, 2H, $NCH_2CHOHCH_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.0 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 155.0 (N*C*=O), 133.1 ($NCO_2CH_2CH{=}CH_2$), 117.6 and 117.1 ($NCO_2CH_2CH{=}CH_2$), 70.3 and 69.7 (NCH_2CHOH), 65.9 and 65.6 ($NCO_2CH_2CH{=}CH_2$), 63.9 and 62.8 ($NCHCH_2$OTBDMS), 57.8 and 57.4 ($NCHCH_2$OTBDMS), 55.7 and 55.2 (NCH_2CHOH), 37.3 and 36.6 ($NCH_2CHOHCH_2$), 25.9 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.5 ($Si(CH_3)_2$); MS (EI), *m/z* (relative intensity) 316 ($M^{+\cdot}$ + 1, 29), 315 ($M^{+\cdot}$, 4), 300 ($M-CH_3$, 26), 284 (4), 261 (8), 260 (50), 259 (100), 258 ($M-OC_3H_5$ or $M-{}^tBu$, 100), 218 (13), 215(10), 214 (52), 200 (12), 170 ($M-CH_2$OTBDMS, 100), 156 (40), 126 (58), 115 (33), 108 (41), 75 (35); IR (Neat) 3422 (br, OH), 2954, 2858, 1682 (C=O), 1467, 1434, 1412 ($SiCH_3$), 1358, 1330, 1255 ($SiCH_3$), 1196, 1180, 1120, 1054, 995, 919, 837, 776, 669 cm^{-1}; exact mass calcd for $C_{15}H_{29}NO_4Si$ *m/e* 315.1866, obsd *m/e* 315.1946.

(2*S*)-*N*-(Allyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-oxopyrrolidine (16).

Method A: A solution of DMSO (12.9 mL, 14.3 g, 183 mmol) in CH_2Cl_2 (90 mL) was added dropwise to a solution of oxalyl chloride (45.1 mL of a 2.0 M solution in CH_2Cl_2, 90.2 mmol) at -60 °C (dry ice/acetone) under a nitrogen atmosphere. After stirring at -70 °C for 30 min, a solution of the alcohol **15** (25.8 g, 81.9 mmol) dissolved in CH_2Cl_2 (215 mL) was added dropwise at -60°C. After 1.5 h at -70°C, the mixture was treated dropwise with TEA (57.2 mL, 41.5 g, 410 mmol) and allowed to warm

to 10°C. The reaction mixture was treated with brine (150 mL) and acidified to pH 3 with conc. HCl. The layers were separated and the organic phase washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash chromatography (40% EtOAc/Petroleum Ether) furnished the ketone **16** as a pale yellow oil (24.24 g, 95%):

Method B: A solution of the alcohol **15** (4.5 g, 14.3 mmol) in CH_2Cl_2 (67.5 mL) was treated with CH_3CN (7.5 mL), 4 Å powdered molecular sieves (3.54 g) and NMO (2.4 g, 20.5 mmol). After 15 min stirring at room temperature, TPAP (0.24 g, 0.7 mmol) was added to the reaction mixture and a colour change (green → black) was observed. The reaction mixture was allowed to stir for a further 2.5 h at which time complete consumption of starting material was observed by TLC (50% EtOAc/Petroleum ether 40 °-60°). The black mixture was concentrated *in vacuo* and the pure ketone **16** was obtained by flash chromatography (50% EtOAc/Petroleum Ether) as a golden oil (4.1 g, 92%): $[\alpha]^{22}_D$ = +1.25 ° (*c* = 10.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 6.0-5.90 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.35-5.22 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.65-4.63 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.48-4.40 (m, 1H, $NCHCH_2OTBDMS$), 4.14-3.56 (m, 4H, $NCH_2C{=}O$ and $NCHCH_2OTBDMS$), 2.74-2.64 (m, 1H, $NCH_2C{=}OCH_2$), 2.46 (d, 1H, *J* = 18.69 Hz, $NCH_2C{=}OCH_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.0 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 210.1 (C=O), 154.1 (NC=O), 132.7 ($NCO_2CH_2CH{=}CH_2$), 118.0 and 117.7 ($NCO_2CH_2CH{=}CH_2$), 66.0 and 65.8 ($NCO_2CH_2CH{=}CH_2$), 65.0 ($NCHCH_2OTBDMS$), 55.7 ($NCHCH_2OTBDMS$), 53.6 ($NCH_2C{=}O$), 40.8 and 40.1 ($NCH_2C{=}OCH_2$), 25.7 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), -5.7 and -5.8 ($Si(CH_3)_2$); MS (CI), *m/z* (relative

intensity) 314 ($M^{+\cdot}$ + 1, 100), 256 (M-OC_3H_5 or M-^tBu, 65); IR (Neat) 2930, 2858, 1767 (C=O), 1709 (NC=O), 1409 ($SiCH_3$), 1362, 1316, 1259 ($SiCH_3$), 1198, 1169, 1103, 1016, 938, 873, 837, 778, 683 cm^{-1}; exact mass calcd for $C_{15}H_{27}NO_4Si$ *m/e* 313.1710, obsd *m/e* 313.1714.

(2*S*)-*N*-(Allyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (17).

Petroleum ether 40°-60° (100 mL) was added to a sample of NaH (0.80 g of a 60% dispersion in oil, 20.12 mmol) and stirred at room temperature under a nitrogen atmosphere. After 0.5 h the mixture was allowed to settle and the Petroleum Ether was transferred from the flask *via* a double-tipped needle under nitrogen. THF (100 mL) was added to the remaining residue and the mixture was cooled to 0°C (ice/acetone). The cool solution was treated dropwise with a solution of methyldiethylphosphonoacetate (3.69 mL, 4.23 g, 20.12 mmol) in THF (100 mL) under nitrogen. After 1 h at room temperature, the mixture was cooled to 0°C and treated dropwise with a solution of the ketone **16** (3.0 g, 9.58 mmol) in THF (30 mL) under nitrogen. After 16 h at room temperature, TLC (50% EtOAc/Petroleum Ether) revealed the complete consumption of ketone and further TLC (5% EtOAc/Petroleum Ether) revealed the formation of mainly the *exo*-product. The reaction mixture was cooled to 0 °C (ice/acetone) and transferred *via* a double-tipped needle under nitrogen to another flask containing NaH (0.40 g of a 60% dispersion in oil, 10.1 mmol) at 0°C, freshly washed as above. The reaction mixture was maintained at 0 °C, and after 40 min TLC revealed the almost

complete conversion to *endo*-product. The THF was evaporated *in vacuo* and the mixture partitioned between saturated $NaHCO_3$ (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 X 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil. Purification by flash chromatography (5% EtOAc/Petroleum Ether) furnished the *endo*-ester **17** (2.22 g, 63%): $[\alpha]^{21}_D = -97.7$ ° (c = 2.78, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 6.47 and 6.42 (br s x 2, 1H, $NCH{=}CCH_2CO_2CH_3$), 5.98-5.86 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.31 (d, 1H, J = 16.85 Hz, $NCO_2CH_2CH{=}CH_2$), 5.22 (d, 1H, J = 10.62 Hz, $NCO_2CH_2CH{=}CH_2$), 4.65-4.49 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.37-4.18 (m, 1H, $NCHCH_2OTBDMS$), 3.76-3.69 (m, 5H, $NCHCH_2OTBDMS$ and CO_2CH_3), 3.09 (br s, 2H, $NCH{=}CCH_2CO_2CH_3$), 2.86-2.80 (m, 1H, $NCH{=}CCH_2CO_2CH_3CH_2$), 2.59 (d, 1H, J = 17.40 Hz, $NCH{=}CCH_2CO_2CH_3CH_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.04 and 0.03 (s x 2, 6H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 171.2 (CO_2CH_3), 151.9 (NC=O), 132.8 ($NCO_2CH_2CH{=}CH_2$), 127.1 and 126.4 ($NCH{=}CCH_2CO_2CH_3$), 118.0 and 117.7 ($NCO_2CH_2CH{=}CH_2$), 114.6 ($NCH{=}CCH_2CO_2CH_3$), 65.9 ($NCO_2CH_2CH{=}CH_2$), 63.4 and 62.6 ($NCHCH_2OTBDMS$), 59.0 and 58.7 ($NCHCH_2OTBDMS$), 51.9 (CO_2CH_3), 36.0 and 34.8 ($NCH{=}CCH_2CO_2CH_3CH_2$), 34.2 and 33.9 ($NCH{=}CCH_2CO_2CH_3$), 25.8 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.4 and -5.5 ($Si(CH_3)_2$); MS (EI), *m/z* (relative intensity) 369 ($M^{+\cdot}$, 58), 354 (28), 326 (31), 312 (M-OC_3H_5 or M-^tBu, 100), 268 (80), 236 (21), 227 (86), 210 (22), 192 (22), 168 (93), 152 (55), 138 (22), 120 (79), 89 (70), 73 (75); IR (NEAT) 3086, 2954, 2930, 2885, 2857, 1744, 1709, 1670, 1463, 1435, 1413, 1362, 1337, 1301, 1253, 1195, 1107, 1064, 1014, 983, 937, 887,

838, 778, 758, 680, 662 555 cm^{-1}; exact mass calcd for $C_{18}H_{31}NO_5Si$ *m/e* 369.1972, obsd *m/e* 369.1868.

(2*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (18)

A catalytic amount of $PdCl_2(PPh_3)_2$ (84 mg, 0.12 mmol) was added to a stirred solution of the allyl carbamate **17** (1.10 g, 2.98 mmol) and H_2O (0.32 mL, 17.8 mmol) in CH_2Cl_2 (36 mL). After 5 min stirring at room temperature, Bu_3SnH (0.89 mL, 0.96 g, 3.30 mmol) was added rapidly in one portion. A slightly exothermic reaction with vigorous gas evolution immediately ensued. The mixture was stirred for 16 h at room temperature under nitrogen at which time TLC (50% EtOAc/Petroleum Ether) revealed the formation of amine along with the complete consumption of starting material. After diluting with CH_2Cl_2 (30 mL), the organic solution was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography (50% EtOAc/Petroleum Ether) to afford the enamine **18** as a slightly orange oil (0.57 g, 67%): ^1H NMR (270 MHz, $CDCl_3$) δ 7.53 and 7.48 (br s x 2, 1H, NC*H*=$CCH_2CO_2CH_3$), 4.35-4.13 (m, 1H, NC*H*CH_2OTBDMS), 3.82-3.17 (m, 7H, NCH=CC$H_2$$CO_2CH_3$, NCHC$H_2$OTBDMS and CO_2CH_3), 2.64-2.04 (m, 2H, NCH=$CCH_2CO_2CH_3$CH_2), 0.90-0.88 (m, 9H, SiC(CH_3)$_3$), 0.09-0.00 (m, 6H, Si(CH_3)$_2$); MS (EI), *m/z* (relative intensity) 285 ($M^{+\cdot}$, 1), 270 ($M-CH_3$, 7), 254 (6), 242 (4), 230 (6), 228 ($M-{}^tBu$, 100), 212 (4), 196 (3), 168 (13), 115 (3), 89 (10), 80 (4), 73 (13); MS (CI), *m/z* (relative intensity) 342 ($M^{+\cdot}$ +57, 7), 302 ($M^{+\cdot}$ +17, 7), 286 ($M^{+\cdot}$ +1, 100), 228 ($M-{}^tBu$, 100).

(2*S*)-*N*-(4-Benzyloxy-5-methoxy-2-nitrobenzoyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (19).

A catalytic amount of DMF (2 drops) was added to a stirred solution of the acid **1** (0.506 g, 1.67 mmol) and oxalyl chloride (0.17 mL, 0.25 g, 1.98 mmol) in CH_2Cl_2 (33 mL). After 16 h at room temperature the acid chloride solution was added dropwise to a stirred mixture of the enamine **18** (0.524 g, 1.84 mmol) and TEA (0.47 g, 0.65 mL, 4.60 mmol) in CH_2Cl_2 (12 mL) at 0°C (ice/acetone) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for a further 2.5 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (50 mL), saturated NH_4Cl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude product as a dark orange oil. Purification by flash chromatography (25% EtOAc/Petroleum Ether) isolated the pure enamide **19** as an orange oil (0.55 g, 58%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (s, $1H_{arom}$), 7.45-7.28 (m, $5H_{arom}$), 6.81 (s, $1H_{arom}$), 5.80 (s, 1H, $NC\mathit{H}{=}CCH_2CO_2CH_3$), 5.22 (s, 2H, $PhC\mathit{H_2}O$), 4.76-4.64 (m, 1H, $NC\mathit{H}CH_2OTBDMS$), 3.97 (s, 3H, $OC\mathit{H_3}$), 3.72-3.66 (m, 5H, $NCHC\mathit{H_2}OTBDMS$ and $CO_2C\mathit{H_3}$), 3.02 (s, 2H, $NCH{=}CC\mathit{H_2}CO_2CH_3$), 3.01-2.63 (m, 2H, $NCH{=}CCH_2CO_2CH_3C\mathit{H_2}$), 0.90 (s, 9H, $SiC(C\mathit{H_3})_3$), 0.11 (s, 6H, $Si(C\mathit{H_3})_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.7 ($\mathit{C}O_2CH_3$), 154.6 ($N\mathit{C}{=}O$), 148.3 (C_{arom}), 137.6 (C_{arom}), 135.2 (C_{arom}), 128.8, 128.5 and 127.6 ($Bn\mathit{C}{-}H_{arom}$), 126.7 (C_{arom}), 126.1 ($N\mathit{C}H{=}CCH_2CO_2CH_3$), 118.8 ($NCH{=}CCH_2CO_2CH_3$), 109.9 ($C{-}H_{arom}$), 109.0 ($C{-}H_{arom}$), 71.3 ($Ph\mathit{C}H_2O$), 60.7 ($NCH\mathit{C}H_2OTBDMS$), 59.0 ($N\mathit{C}HCH_2OTBDMS$), 56.7 ($O\mathit{C}H_3$), 52.0 ($CO_2\mathit{C}H_3$), 35.1 ($NCH{=}C\mathit{C}H_2CO_2CH_3$), 33.8 ($NCH{=}CCH_2CO_2CH_3\mathit{C}H_2$), 25.8

($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.3 and -5.4 ($Si(CH_3)_2$).

(2*S*)-*N*-(4-Benzyloxy-5-methoxy-2-nitrobenzoyl)-2-(hydroxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (20).

A solution of the silyl protected compound **274** (0.45 g, 0.79 mmol) in THF (8 mL) was treated with H_2O (8 mL) and glacial acetic acid (24 mL). After 5 h stirring at room temperature TLC (50% EtOAc/Petroleum Ether) showed the complete consumption of starting material. The mixture was carefully added dropwise to a stirred solution of $NaHCO_3$ (64 g) in H_2O (640 mL) and extracted with EtOAc (3 X 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an orange glass. Purification by flash chromatography (80% EtOAc/Petroleum Ether) furnished the pure alcohol **20** as a light orange glass (0.35 g, 98%): ^1H NMR (270 MHz, $CDCl_3$) δ 7.78 (s, $1H_{arom}$), 7.48-7.33 (m, $5H_{arom}$), 6.86 (s, $1H_{arom}$), 5.82 (s, 1H, $NCH{=}CCH_2CO_2CH_3$), 5.22 (s, 2H, $PhCH_2O$), 4.81-4.71 (m, 1H, $NCHCH_2OH$), 3.98-3.92 (m, 5H, $NCHCH_2OH$ and OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.10-2.22 (m, 3H, $NCH{=}CCH_2CO_2CH_3$ and $NCH{=}CCH_2CO_2CH_3CH_2$), 2.50-2.35 (m, 1H, $NCH{=}CCH_2CO_2CH_3CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.6 (CO_2CH_3), 154.8 (NC=O), 148.5 (C_{arom}), 137.5 (C_{arom}), 135.1 (C_{arom}), 128.9, 128.6 and 127.6 ($BnC\text{-}H_{arom}$), 126.2 ($NCH{=}CCH_2CO_2CH_3$), 119.4 ($NCH{=}CCH_2CO_2CH_3$), 109.8 ($C\text{-}H_{arom}$), 109.0 ($C\text{-}H_{arom}$), 71.4 ($PhCH_2O$), 61.5 ($NCHCH_2OH$), 61.4 ($NCHCH_2OH$), 56.8 (OCH_3), 52.1 (CO_2CH_3), 35.6 ($NCH{=}CCH_2CO_2CH_3$), 33.5 ($NCH{=}CCH_2CO_2CH_3CH_2$); MS (EI), *m/z* (relative intensity) 456 ($M^{+\cdot}$, 7), 286 ($M\text{-}NCHC{=}CH_2CO_2CH_3CH_2CHCH_2OH$, 25), 270 ($NCHC{=}CH_2CO_2CH_3CH_2CHCH_2OH$, 6), 91 ($PhCH_2$, 100), 80 (6); exact mass

calcd for $C_{23}H_{24}N_2O_8$ *m/e* 456.1533, obsd *m/e* 456.1557.

(2*S*)-*N*-(2-Amino-4-benzyloxy-5-methoxybenzoyl)-2-(hydroxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (21).

A solution of the nitro-alcohol **20** (0.35 g, 0.77 mmol) and $SnCl_2/2H_2O$ (0.87 g, 3.86 mmol) in methanol (16 mL) was heated to reflux and monitored by TLC (90% $CHCl_3$/MeOH). After 1 h the MeOH was evaporated *in vacuo* and the resulting residue cooled (ice), and treated carefully with saturated $NaHCO_3$ (65 mL). The mixture was diluted with EtOAc (65 mL), and after 16 h stirring at room temperature the inorganic precipitate was removed by filtration through celite. The organic layer was separated, washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude amine **21** as a pale orange glass (0.29 g, 88%) which was carried through to the next step without further purification or analysis due to the instability of the amine.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-2-(hydroxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (22).

A solution of the amino-alcohol **21** (0.29 g, 0.68 mmol) in CH_2Cl_2 (12 mL) was cooled to 0°C (ice/acetone) and treated with pyridine (0.11 mL, 0.11 g, 1.39 mmol). A solution of allyl chloroformate (79 μL, 90 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was then added dropwise to the stirred mixture. The reaction mixture was allowed to warm to room temperature and stirred for a further 2.5 h, at which point TLC (EtOAc) revealed complete consumption of

the amine **21**. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $CuSO_4$ (20 mL), H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (70% EtOAc/Petroleum Ether) to afford the pure alloc-amino compound **22** as a colourless glass (0.14 g, 40%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.58 (br s, 1H, N*H*), 7.88 (br s, $1H_{arom}$), 7.50-7.29 (m, $5H_{arom}$), 6.83 (s, $1H_{arom}$), 6.42 (br s, 1H, $NCH{=}CCH_2CO_2CH_3$), 6.03-5.89 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.39-5.22 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 5.18 (s, 2H, $PhCH_2O$), 4.77-4.73 (m, 1H, $NCHCH_2OH$), 4.65-4.62 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.32-3.84 (m, 5H, $NCHCH_2OH$ and OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.09 (s, 2H, $NCH{=}CCH_2CO_2CH_3$), 3.05-2.95 (m, 1H, $NCH{=}CCH_2CO_2CH_3CH_2$), 2.35 (dd, 1H, J = 3.76, 16.72 Hz, $NCH{=}CCH_2CO_2CH_3CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.6 (CO_2CH_3), 167.4 ($NC{=}O_{amide}$), 153.5 ($NC{=}O_{carbamate}$), 151.1 (C_{arom}), 144.4 (C_{arom}), 136.1 (C_{arom}), 132.6 (C_{arom}), 132.4 ($NCO_2CH_2CH{=}CH_2$), 128.6, 128.1 and 127.7 ($BnC{-}H_{arom}$), 118.5 ($NCH{=}CCH_2CO_2CH_3$), 118.2 ($NCO_2CH_2CH{=}CH_2$), 112.1 ($C{-}H_{arom}$), 106.3 ($C{-}H_{arom}$), 70.7 ($PhCH_2O$), 66.5 ($NCHCH_2OH$), 65.9 ($NCO_2CH_2CH{=}CH_2$), 61.9 ($NCHCH_2OH$), 56.7 (OCH_3), 52.1 (CO_2CH_3), 35.6 ($NCH{=}CCH_2CO_2CH_3$), 33.6 ($NCH{=}CCH_2CO_2CH_3CH_2$); MS (FAB), *m/z* (relative intensity) 618 ($M^{+\cdot}$ + Thioglycerol, 2), 511 ($M^{+\cdot}$ + 1, 5), 510 ($M^{+\cdot}$, 1), 340 ($M{-}NCH{=}CCH_2CO_2CH_3CH_2CHCH_2OH$, 20), 300 (3), 282 (14), 256 (7), 192 (6), 171 (16), 149 (22), 140 (12), 112 (4), 91 ($PhCH_2$, 100), 80 (6), 65 (1), 57 (3).

(11*S*,11a*S*)-10-Allyloxycarbonyl-8-benzyloxy-11-hydroxy-7-methoxy-2-(methoxycarbonylmethyl)-1,10,11,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (23).

A solution of the alcohol **22** (0.14 g, 0.28 mmol) in CH_2Cl_2/CH_3CN (12 mL, 3:1) was treated with 4 Å powdered molecular sieves (0.15 g) and NMO (49 mg, 0.42 mmol). After 15 min stirring at room temperature, TPAP (4.90 mg, 14 μmol) was added and stirring continued for a further 1 h 30 min at which point TLC (80% EtOAc/Petroleum Ether) showed product formation along with some unoxidised starting material. The mixture was then treated with a further quantity of NMO (49 mg, 0.42 mmol) and TPAP (4.9 mg, 14 μmol), and allowed to stir for a further 0.5 h when TLC revealed reaction completion. The mixture was evaporated *in vacuo* onto silica and subjected to flash chromatography (60% EtOAc/Petroleum Ether) to provide the protected carbinolamine **23** as a colourless glass (39 mg, 28%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.43–7.25 (m, $6H_{arom}$), 6.90 (br s, $1H_{arom}$), 6.74 (s, 1H, $NCH{=}CCH_2CO_2CH_3$), 5.79–5.64 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.77 (d, 1H, J = 10.26 Hz, NCHC*H*OH), 5.19–5.06 (m, 4H, $NCO_2CH_2CH{=}CH_2$ and $PhCH_2O$), 4.64–4.45 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 4.18–3.83 (m, 4H, OCH_3 and NC*H*CHOH), 3.71 (s, 3H, CO_2CH_3), 3.19 (s, 2H, $NCH{=}CCH_2CO_2CH_3$), 3.09 (dd, 1H, J = 11.09, 16.70 Hz, $NCH{=}CCH_2CO_2CH_3CH_2$), 2.74 (d, 1H, J = 17.03 Hz, $NCH{=}CCH_2CO_2CH_3CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.7 (CO_2CH_3), 163.3 ($NC{=}O_{amide}$), 155.9 ($NC{=}O_{carbamate}$), 150.3 (C_{arom}), 149.1 (C_{arom}), 136.1 (C_{arom}), 131.8 ($NCO_2CH_2CH{=}CH_2$), 128.7, 128.2 and 127.3 ($BnC{-}H_{arom}$), 126.2 ($NCH{=}CCH_2CO_2CH_3$), 125.1 (C_{arom}), 118.1 ($NCO_2CH_2CH{=}CH_2$), 117.7 ($NCH{=}CCH_2CO_2CH_3$), 114.7 ($C{-}H_{arom}$), 111.0 ($C{-}H_{arom}$), 85.9 (NCH*C*HOH), 71.1 ($PhCH_2O$), 66.8 ($NCO_2CH_2CH{=}CH_2$), 59.5

(N*C*HCHOH), 56.2 (O*C*H_3), 52.1 (CO_2*C*H_3), 37.0 (NCH=C*C*$H_2CO_2CH_3$), 33.7 (NCH=$CH_2CO_2CH_3$*C*H_2); MS (EI), *m/z* (relative intensity) 508 ($M^{+\cdot}$, 16), 449 (3), 422 (3), 404 (2), 368 (3), 340 (19), 324 (2), 282 (6), 255 (2), 225 (1), 206 (2), 192 (3), 169 (4), 152 (2), 140 (10), 131 (5), 108 (5), 91 ($PhCH_2$, 100), 80 (9), 57 (9); IR (NUJOL®) 3600-2500 (br, OH), 2924, 2853, 2360, 1715, 1602, 1514, 1462, 1377, 1271, 1219, 1169, 1045, 722, 699; exact mass calcd for $C_{27}H_{28}N_2O_8$ *m/e* 508.1846, obsd *m/e* 508.1791.

(11*S*,11a*S*)&(11*R*,11a*S*)-8-Benzyloxy-7,11-dimethoxy-2-(methoxycarbonylmethyl)-1,10,11,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (25, SJG-245).

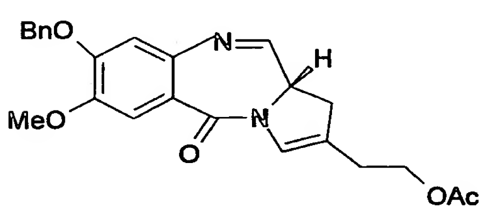
A catalytic amount of tetrakis(triphenylphosphine)palladium (5.0 mg, 4.33 μmol) was added to a stirred solution of the Alloc-protected carbinolamine **23** (88 mg, 0.17 mmol), triphenylphosphine (2.27 mg, 8.65 μmol) and pyrrolidine (13 mg, 0.18 mmol) in CH_2Cl_2 (15 mL). After 2 h stirring at room temperature under a nitrogen atmosphere, TLC (80% EtOAc/Petroleum Ether) revealed the complete consumption of starting material. The solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (60% EtOAc/Petroleum Ether) to afford the novel PBD (SJG-245) as a colourless glass (54 mg, 77%) which was repeatedly evaporated *in vacuo* with $CHCl_3$ in order to provide the N10-C11 imine form **24**: ^{1}H NMR (270 MHz, $CDCl_3$) (imine) δ 7.80 (d, 1H, *J* = 4.03 Hz, *H*C=N), 7.50 (s, $1H_{arom}$), 7.45-7.26 (m, $5H_{arom}$), 6.91 (br s, 1H, NC*H*=$CCH_2CO_2CH_3$), 6.83 (s, $1H_{arom}$), 5.21-5.12 (m, 2H, PhC*H_2*O), 3.94 (s, 3H, OC*H_3*), 3.73 (s, 3H, CO_2C*H_3*), 3.23 (s, 2H, NCH=CC*H_2*CO_2CH_3), 3.15 (m, 2H, NCH=$CCH_2CO_2CH_3$C*H_2*); ^{13}C NMR (67.8 MHz, $CDCl_3$) (imine)

δ 170.7 (CO_2CH_3), 162.7 (HC=N), 161.4 (NC=O), 150.9 (C_{arom}), 148.1 (C_{arom}), 140.1 (C_{arom}), 136.0 (C_{arom}), 128.7, 128.2 and 127.3 (BnC-H_{arom}), 127.3 ($NCH=CCH_2CO_2CH_3$), 119.2 (C_{arom}), 117.5 ($NCH=CCH_2CO_2CH_3$), 111.8 (C-H_{arom}), 111.5 (C-H_{arom}), 70.8 ($PhCH_2O$), 56.2 (OCH_3), 53.8 (NCHHC=N), 52.0 (CO_2CH_3), 37.4 ($NCH=CCH_2CO_2CH_3$), 33.6 ($NCH=CCH_2CO_2CH_3CH_2$).

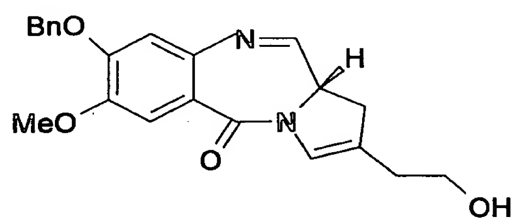
Repeated evaporation *in vacuo* of **24** with CH_3OH provided the N10-C11 methyl ether forms **25**: ^1H NMR (270 MHz, CD_3OD) (11*S*,11a*S* isomer) δ 7.44-7.25 (m, $5H_{arom}$), 7.16 (s, $1H_{arom}$), 6.85 (br s, 1H, $NCH=CCH_2CO_2CH_3$), 6.62 (s, $1H_{arom}$), 5.09 (s, 2H, $PhCH_2O$), 4.52 (d, 1H, J = 8.80 Hz, $NCHCHOCH_3$), 4.00-3.85 (m, 1H, $NCHCHOCH_3$), 3.80 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.41 (s, 3H, $NCHCHOCH_3$), 3.24 (br s, 2H, $NCH=CCH_2CO_2CH_3$), 3.20-3.00 (m, 1H, $NCH=CCH_2CO_2CH_3CH_2$), 2.60-2.50 (m, 1H, $NCH=CCH_2CO_2CH_3CH_2$); ^{13}C NMR (67.8 MHz, CD_3OD) (11*S*,11a*S* isomer) δ 172.7 (CO_2CH_3), 166.8 (C_{arom}), 153.3 (NC=O), 146.4 (C_{arom}), 139.7 (C_{arom}), 138.0 (C_{arom}), 132.4 (C_{arom}), 129.6, 129.1 and 128.8 (BnC-H_{arom}), 127.0 ($NCH=CCH_2CO_2CH_3$), 120.8 ($NCH=CCH_2CO_2CH_3$), 113.7 (C-H_{arom}), 109.2 (C-H_{arom}), 97.1 ($NCHCHOCH_3$), 71.7 ($PhCH_2O$), 60.2 ($NCHCHOCH_3$), 56.8 (OCH_3), 55.2 ($NCHCHOCH_3$), 52.5 (CO_2CH_3), 38.7 ($NCH=CCH_2CO_2CH_3$), 34.1 ($NCH=CCH_2CO_2CH_3CH_2$); MS (EI), *m/z* (relative intensity) 420 ($M^{+\cdot}$, methyl ether, 1), 418 (methyl ether - 2, 2), 406 ($M^{+\cdot}$, imine, 23), 404 (41), 375 (2), 345 (6), 333 (7), 313 (22), 299 (10), 285 (6), 253 (6), 242 (4), 225 (2), 214 (2), 198 (2), 183 (4), 168 (2), 155 (6), 136 (3), 105 (3), 91 ($PhCH_2$, 100), 80 (4), 65 (7); IR (NUJOL®) 3318 (br, OH of carbinolamine form), 2923, 2853, 1737, 1692, 1658, 1627, 1601, 1552, 1511, 1501, 1464, 1461,

1452, 1378, 1244, 1072, 1006, 786, 754, 698 cm^{-1}; exact mass calcd for $C_{23}H_{22}N_2O_5$ *m/e* 406.1529, obsd *m/e* 406.1510.

Examples 1(c&d): Synthesis of SJG-301 (UP2051) and SJG-303 (UP2052) (see Figure 3)



Example 1(c)



Example 1(d)

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (26)

Petroleum Ether (100 mL) was added to a sample of NaH (1.41 g of a 60% dispersion in oil, 35.25 mmol) and stirred at room temperature under a nitrogen atmosphere. After 0.5 h the mixture was allowed to settle and the Petroleum Ether was transferred from the flask *via* a double-tipped needle under nitrogen. THF (80 mL) was added to the remaining residue and the mixture was cooled to 0 °C (ice/acetone). The cool solution was treated dropwise with a solution of methyldiethylphosphonoacetate (6.47 mL, 7.41 g, 35.25 mmol) in THF (80 mL) under nitrogen. After 1.5 h at room temperature, the mixture was cooled to 0°C and treated dropwise with a solution of the ketone **6** (8.0 g, 14.1 mmol) in THF (50 mL) under nitrogen. After 16 h at room temperature, TLC (20% EtOAc/Petroleum Ether) revealed reaction

completion. The THF was evaporated *in vacuo* and the mixture partitioned between saturated $NaHCO_3$ (200 mL) and EtOAc (220 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 X 200 mL). The combined organic layers were washed with H_2O (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark red oil. Purification by flash chromatography (15% EtOAc/Petroleum Ether) furnished the *endo*-ester **26** (7.02 g, 80%): $[\alpha]^{22}_D = -93.0\ °$ (c = 1.04, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 7.95 (s, 1H), 7.50-7.29 (m, 5H), 6.82 (s, 1H), 6.46 (br s, 1H), 6.02-5.88 (m, 1H), 5.35 (dd, 1H, J = 2.93, 17.22 Hz), 5.24 (d, 1H, J = 10.44 Hz), 5.18 (s, 2H), 4.70-4.61 (m, 3H), 3.96-3.82 (m, 5H), 3.68 (s, 3H), 3.08 (s, 2H), 2.91-2.82 (m, 1H), 2.71-2.65 (m, 1H), 0.88 (s, 9H), 0.06 and 0.04 (s x 2, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.7, 165.8, 153.5, 150.6, 144.0, 136.2, 132.7, 132.5, 128.6, 128.2, 128.1, 127.7, 118.1, 118.0, 114.4, 112.0, 106.0, 70.6, 65.7, 62.3, 59.4, 56.6, 52.0, 34.6, 33.9, 25.8, 18.1, -5.4; MS (EI), m/z (relative intensity) 626 ($M^{+\cdot}$ + 1, 3), 625 ($M^{+\cdot}$ + 1, 7), 624 ($M^{+\cdot}$, 14), 568 (5), 567 (11), 509 (3), 476 (3), 341 (5), 340 (17), 339 (4), 299 (3), 286 (18), 285 (87), 282 (11), 256 (4), 242 (3), 229 (3), 228 (14), 226 (11), 168 (10), 166 (3), 152 (6), 141 (5), 140 (50), 139 (9), 108 (3), 92 (10), 91 (100), 89 (6), 80 (11), 75 (11), 73 (10), 65 (5), 57 (6), 41 (12); IR (NEAT) 3332 (br, NH), 3019, 2953, 2930, 2857, 1733, 1622, 1599, 1524, 1491, 1464, 1408, 1362, 1335, 1258, 1205, 1171, 1113, 1051, 1027, 938, 839, 757, 697, 666 cm^{-1}; exact mass calcd for $C_{33}H_{44}N_2O_8Si$ m/e 624.2867, obsd m/e 624.2936.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-(hydroxy-2-ethyl)-2,3-dihydropyrrole (27)

A solution of the ester **26** (4.0 g, 6.41 mmol) in THF (55 mL) was cooled to 0°C (ice/acetone) and treated with $LiBH_4$ (0.21 g, 9.62 mmol) in portions. The mixture was allowed to warm to room temperature and stirred under a nitrogen atmosphere for 26 h at which point TLC (50% EtOAc/Petroleum Ether) revealed the complete consumption of starting material. The mixture was cooled to 0°C (ice/acetone) and water (14 mL) was carefully added. Following evaporation of the THF *in vacuo*, the mixture was cooled and then neutralised with 1 N HCl. The solution was then diluted with H_2O (100 mL) and extracted with EtOAc (3 X 100 mL), the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude oil was purified by flash chromatography (30 → 40% EtOAc/Petroleum Ether) to furnish the pure *endo*-alcohol **27** as a transparent yellow oil (2.11 g, 55%): $[\alpha]^{22}{}_D$ = -86.43 ° (c = 1.38, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 7.92 (br s, 1H), 7.50-7.28 (m, 5H), 6.82 (s, 1H), 6.36 (br s, 1H), 6.02-5.87 (m, 1H), 5.35 (d, 1H, J = 17.22 Hz), 5.24 (d, 1H, J = 11.72 Hz), 5.18 (s, 2H), 4.64-4.61 (m, 3H), 4.10-3.99 (m, 1H), 3.80 (s, 3H), 3.79-3.66 (m, 3H), 2.85-2.75 (m, 1H), 2.64-2.60 (m, 1H), 2.30 (t, 2H, J = 6.23 Hz), 1.74 (br s, 1H), 0.88 (s, 9H), 0.06 and 0.04 (s x 2, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.3, 153.5, 150.5, 144.2, 136.3, 132.5, 128.6, 128.1, 127.7, 126.7, 122.8, 118.0, 114.3, 112.0, 106.1, 70.7, 65.7, 62.8, 60.4, 59.1, 56.6, 34.4, 31.7, 25.8, 18.2, -5.4; MS (EI), m/z (relative intensity) 598 ($M^{+\cdot}$ + 2, 3), 597 ($M^{+\cdot}$ + 1, 5), 596

($M^{+\cdot}$, 13), 581 (2), 541 (2), 540 (4), 539 (9), 448 (2), 341 (2), 340 (12), 282 (7), 259 (5), 258 (20), 257 (100), 256 (3), 227 (3), 226 (12), 200 (5), 168 (6), 124 (3), 113 (3), 112 (50), 111(4), 94 (10), 91 (25), 73 (3); IR (NEAT) 3340 (br), 3066, 3033, 2930, 2857, 1732, 1598, 1520, 1456, 1409, 1328, 1205, 1166, 1113, 1049, 1023, 938, 839, 778, 744, 697, 677, 637 cm^{-1}.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-4-(acyloxy-2-ethyl)-2-(*tert*-butyldimethylsilyloxymethyl)-2,3-dihydropyrrole (28)

Acetic anhydride (8.17 g, 7.55 mL, 80 mmol) and pyridine (30.2 mL) were added to the alcohol **27** (0.953 g, 1.60 mmol) and the solution stirred for 16 h under nitrogen at which point TLC revealed reaction completion (50% EtOAc/Petroleum Ether). The reaction mixture was cooled to 0°C (ice/acetone) and treated dropwise with MeOH (15 mL). After stirring at room temperature for 1 h the mixture was treated dropwise with H_2O (30.2 mL) and allowed to stir for a further 16 h. Following dilution with EtOAc (56 mL), the solution was cooled to 0°C and treated dropwise with 6 N HCl (56 mL). The layers were separated and the organic phase was washed with 6N HCl (2 X 28 mL) and the combined aqueous layers were then extracted with EtOAc (70 mL). The combined organic phases were then washed with H_2O (60 mL), brine (60 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude oil was a mixture of the desired product **28** and the TBDMS cleaved compound **29** as judged by TLC. Purification by flash chromatography (20 - 100% EtOAc/Petroleum Ether) provided **29** (0.2 g) and desired acyl-TBDMS compound **28** (0.59 g, 58%) as a

colourless oil: $[\alpha]^{22}_{D}$ = -87.04 ° (c = 4.91, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 8.77 (br s, 1H), 7.94 (br s, 1H), 7.49-7.31 (m, 5H), 6.80 (s, 1H), 6.37 (br s, 1H), 6.02-5.89 (m, 1H), 5.35 (dd, 1H, J = 17.22, 1.65 Hz), 5.24 (d, 1H, J = 10.30 Hz), 5.19 (s, 2H), 4.64-4.61 (m, 3H), 4.12 (t, 2H, J = 6.78 Hz), 4.03-3.95 (m, 1H), 3.83-3.75 (m, 4H), 2.85-2.75 (m, 1H), 2.64-2.60 (m, 1H), 2.40-2.26 (m, 2H,), 2.03 (s, 3H), 0.88 (s, 9H), 0.04, 0.01 and -0.01(s x 3, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.9, 165.5, 153.5, 150.6, 144.1, 136.3, 132.7, 132.5, 128.6, 128.1, 127.7, 126.5, 122.2, 118.0, 114.3, 112.2, 106.1, 70.7, 65.7, 62.4, 60.4, 59.2, 56.7, 34.6, 31.7, 27.9, 25.8, 20.9, 18.2, -5.4; MS (EI), m/z (relative intensity) 640 ($M^{+\cdot}$ + 2, 3), 639 ($M^{+\cdot}$ + 1, 7), 638 ($M^{+\cdot}$, 15), 623 (2), 583 (3), 582 (6), 581 (14), 539 (2), 523 (3), 490 (3), 341 (5), 340 (22), 301 (5), 300 (18), 299 (75), 283 (3), 282 (14), 256 (4), 242 (7), 241 (5), 240 (16), 239 (62), 226 (6), 192 (3), 182 (8), 181 (5), 180 (3), 168 (5), 166 (5), 154 (10), 131 (3), 106 (3), 95 (4), 94 (48), 93 (5), 92 (8), 91 (100), 89 (5), 75 (6), 73 (8), 65 (3), 57 (3); IR (NEAT) 3324 (br, NH), 3066, 3018, 2954, 2930, 2857, 1737, 1622, 1598, 1523, 1489, 1464, 1409, 1363, 1327, 1230, 1205, 1168, 1115, 1080, 1030, 994, 937, 839, 756, 697, 667, 638, 606, 472, 459, 443 cm^{-1}; exact mass calcd for $C_{34}H_{46}N_2O_8Si$ m/e 638.3024, obsd m/e 638.3223.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-4-(acyloxy-2-ethyl)-2-(hydroxymethyl)-2,3-dihydropyrrole (29)

A solution of the silyl ether **28** (0.83 g, 1.30 mmol) in THF (14 mL) was treated with H_2O (14 mL) and glacial acetic acid (42 mL). After 2 h stirring at room temperature TLC (50%

EtOAc/Petroleum Ether) showed the complete consumption of starting material. The mixture was cooled (ice) and treated dropwise with a solution of $NaHCO_3$ (64 g) in H_2O (640 mL). The aqueous solution was extracted with EtOAc (3 X 100 mL) and the combined organic layers were washed with H_2O (150 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an orange oil. Purification by flash chromatography (60% EtOAc/Petroleum Ether) furnished the pure alcohol **29** as a white glass (0.537 g, 81%): $[\alpha]^{21}_D$ = -83.60 ° (*c* = 0.25, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.89 (br s, 1H), 7.49-7.29 (m, 5H), 6.81 (s, 1H), 6.28 (br s, 1H), 6.03-5.89 (m, 1H), 5.35 (ddd, 1H, *J* = 17.22, 3.11, 1.46, Hz), 5.25 (d, 1H, *J* = 10.44 Hz), 5.19 (s, 2H), 4.80-4.70 (m, 1H), 4.65-4.62 (m, 2H), 4.41-4.31 (m, 1H), 4.20-4.06 (m, 2H,), 3.84-3.77 (m, 5H), 2.98-2.88 (m, 1H), 2.39 (t, 2H, *J* = 6.51 Hz), 2.33-2.25 (m, 1H,), 2.03 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.8, 167.1, 153.5, 151.0, 144.3, 136.1, 132.6, 132.4, 128.6, 128.1, 127.7, 126.3, 122.6, 118.1, 112.2, 106.3, 70.7, 66.5, 65.8, 62.0, 61.7, 56.8, 35.4, 31.7, 27.8, 20.9; MS (EI), *m/z* (relative intensity) 525 ($M^{+\cdot}$ + 1, 5), 524 ($M^{+\cdot}$, 14), 341 (5), 340 (16), 299 (2), 283 (3), 282 (14), 256 (4), 227 (5), 208 (2), 192 (3), 190 (2), 186 (9), 185 (60), 168 (2), 167 (5), 166 (2), 164 (2), 163 (2), 154 (3), 136 (3), 131 (3), 126 (7), 125 (53), 108 (2), 107 (2), 106 (2), 105 (3), 95 (3), 94 (19), 93 (3), 92 (9), 91 (100), 83 (2), 69 (2), 68 (3), 67 (3), 65 (5), 58 (6), 57 (17) ; IR ($CHCl_3$) 3335 (br), 2933, 1732, 1599, 1524, 1455, 1434, 1408, 1231, 1170, 1112, 1029, 995, 932, 868, 765, 698, 638, 606 cm^{-1}; exact mass calcd for $C_{28}H_{32}N_2O_8$ *m/e* 524.2159, obsd *m/e* 524.2074.

(11*S*,11a*S*)-2-(Acyloxy-2-ethyl)-10-allyloxycarbonyl-8-benzyloxy-11-hydroxy-7-methoxy-1,10,11,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (30)

Method A: A solution of DMSO (0.25 mL, 0.27 g, 3.49 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 35 min to a solution of oxalyl chloride (0.87 mL of a 2.0 M solution in CH_2Cl_2, 1.75 mmol) at -45°C (liq.N_2/Chlorobenzene) under a nitrogen atmosphere. After stirring at -45°C for 40 min, a solution of the alcohol **29** (0.51 g, 0.97 mmol) in CH_2Cl_2 (7 mL) was added dropwise over 35 min at -45°C. After 55 min at -45°C, the mixture was treated dropwise with a solution of TEA (0.57 mL, 0.41 g, 4.10 mmol) in CH_2Cl_2 (5 mL) over 40 min at -45°C. After a further 45 min, the reaction mixture was allowed to warm to room temperature and was diluted with CH_2Cl_2 (60 mL), washed with 1N HCl (60 mL), H_2O (60 mL), brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. TLC (80% EtOAc/Petroleum Ether) of the crude material revealed complete reaction. Purification by flash chromatography (50% EtOAc/Petroleum Ether) furnished the protected carbinolamine **30** as a creamy glass (0.25 g, 49%).

Method B: A solution of the alcohol **29** (0.21 g, 0.40 mmol) in CH_2Cl_2/CH_3CN (30 mL, 3:1) was treated with 4 Å powdered molecular sieves (0.15 g) and NMO (69 mg, 0.59 mmol). After 15 min stirring at room temperature, TPAP (6.9 mg, 19.8 µmol) was added and stirring continued for a further 1 h at which point TLC (80% EtOAc/Petroleum Ether) showed product formation along with some unoxidised starting material. The mixture was then treated with a further quantity of NMO (35 mg, 0.30 mmol) and TPAP (3.50 mg,

10 μmol), and allowed to stir for a further 1.5 h after which time TLC revealed complete reaction. The mixture was evaporated *in vacuo* onto silica and subjected to flash chromatography (50% EtOAc/Petroleum Ether) to provide the protected carbinolamine **30** as a creamy glass (95 mg, 46%): $[\alpha]^{20}_{D}$ = +113.85 ° (*c* = 0.95, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.49-7.26 (m, 6H), 6.80 (s, 1H), 6.76 (s, 1H), 5.79-5.59 (m, 1H), 5.75 (d, 1H, *J* = 10.08 Hz), 5.19-5.05 (m, 4H), 4.52-4.29 (m, 2H), 4.28-4.08 (m, 3H), 3.95-3.80 (m, 4H), 2.99 (dd, 1H, *J* = 10.72, 16.94 Hz), 2.66 (d, 1H, *J* = 16.86 Hz), 2.46 (t, 2H, *J* = 6.41 Hz), 2.06 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.1, 163.1, 155.9, 150.3, 149.1, 136.1, 131.8, 128.7, 128.6, 128.2, 127.3, 125.3, 124.4, 121.6, 118.0, 114.8, 111.0, 85.9, 71.1, 66.8, 62.0, 70.7, 59.4, 56.2, 37.0, 27.9, 21.0; MS (EI), *m/z* (relative intensity) 522 ($M^{+\cdot}$, 13), 463 (9), 462 (13), 341 (8), 340 (32), 282 (11), 256 (3), 183 (5), 154 (3), 123 (8), 94 (20), 91 (100), 65 (4), 57 (15); exact mass calcd for $C_{28}H_{30}N_2O_8$ *m/e* 522.2002, obsd *m/e* 522.2008.

Example 1(c): (11a*S*)-2-(Acyloxy-2-ethyl)-8-benzyloxy-7-methoxy-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (31,UP2051, SJG-301)

A catalytic amount of tetrakis(triphenylphosphine)palladium (5.26 mg, 4.55 μmol) was added to a stirred solution of the Alloc-protected carbinolamine **30** (95 mg, 0.18 mmol), triphenylphosphine (2.39 mg, 9.10 μmol) and pyrrolidine (13.6 mg, 0.19 mmol) in CH_2Cl_2 (10 mL). After 1 h stirring at room temperature under a nitrogen atmosphere, TLC (97% $CHCl_3$/MeOH) revealed the complete consumption of starting material. The solvent was evaporated *in*

vacuo and the crude residue was purified by flash chromatography (99.5% $CHCl_3$/MeOH) to afford the PBD **(31, SJG-301, UP2051)** as an orange glass which was repeatedly evaporated *in vacuo* with $CHCl_3$ in order to provide the N10-C11 imine form (66.3 mg, 87%): $[\alpha]^{21}_D$ = +741.67 ° (*c* = 0.66, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (imine) δ 7.78 (d, 1H, *J* = 4.03 Hz), 7.70-7.28 (m, 6H), 6.83 (s, 1H), 6.82 (s, 1H), 5.19-5.18 (m, 2H), 4.27-4.16 (m, 2H), 3.94 (s, 3H), 3.44-3.35 (m, 1H), 3.28-3.15 (m, 1H), 3.04-2.97 (m, 1H), 2.52-2.47 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 170.9, 162.6, 161.1, 150.9, 148.2, 140.1, 136.1, 132.1, 132.0, 128.7, 128.6, 128.1, 127.3, 124.7, 121.4, 111.9, 111.6, 70.8, 61.9, 56.2, 53.6, 37.4, 27.9, 21.0; MS (EI), *m/z* (relative intensity) 421 ($M^{+\cdot}$ + 1, 4), 420 ($M^{+\cdot}$, 14), 419 (12), 418 (36), 361 (6), 360 (20), 328 (3), 313 (8), 270 (4), 269 (7), 268 (9), 267 (22), 256 (4), 129 (3), 105 (3), 94 (4), 93 (3), 92 (12), 91 (100), 83 (3), 80 (3), 73 (5), 71 (3), 69 (3), 65 (5), 60 (4), 57 (5), 55 (4); IR ($CHCl_3$) 3313 (br), 2957, 2934, 1736, 1598, 1509, 1455, 1437, 1384, 1243, 1179, 1120, 1096, 1037, 753, 696, 666, 542 cm^{-1}; exact mass calcd for $C_{24}H_{24}N_2O_5$ *m/e* 420.1685, obsd *m/e* 420.1750.

(11*S*,11a*S*)-10-Allyloxycarbonyl-8-benzyloxy-11-hydroxy-2-(hydroxy-2-ethyl)-7-methoxy-1,10,11,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (32).

A solution of K_2CO_3 (328 mg, 2.38 mmol) in H_2O (6 mL) was added dropwise to a stirred solution of the acyl compound **30** (0.248 g, 0.475 mmol) in CH_2Cl_2 (3 mL) and MeOH (8 mL). After stirring for 16 h at room temperature TLC (EtOAc) revealed complete reaction.

The $MeOH/CH_2Cl_2$ was evaporated *in vacuo* to give a cloudy aqueous solution which was diluted with H_2O (30 mL) and extracted with EtOAc (3 X 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide a creamy oil. Purification by flash chromatography (97% $CHCl_3/MeOH$) furnished the homoallylic alcohol **32** as a transparent colourless glass (178 mg, 78%): $[\alpha]^{21}_D$ = +48.43 ° (c = 1.56, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.43-7.24 (m, 6H), 6.84 (s, 1H), 6.73 (s, 1H), 5.74-5.55 (m, 1H), 5.73 (d, 1H, J = 8.79 Hz), 5.19-5.06 (m, 4H), 4.46-4.23 (m, 2H), 3.92-3.70 (m, 6H), 3.07-2.97 (m, 1H), 2.67 (d, 1H, J = 16.49 Hz), 2.40-2.17 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 163.1, 155.8, 150.3, 149.1, 136.1, 131.8, 128.6, 128.1, 127.7, 127.4, 125.3, 124.1, 124.0, 123.1, 123.0, 117.9, 114.9, 110.9, 86.0, 71.1, 66.7, 60.3, 59.6, 56.2, 37.1, 31.5; MS (EI), *m/z* (relative intensity) 482 ($M^{+\cdot}$ + 2, 4), 481 ($M^{+\cdot}$ + 1, 10), 480 ($M^{+\cdot}$, 26), 449 (4), 378 (12), 347 (7), 341 (7), 340 (25), 339 (4), 284 (4), 282 (10), 143 (4), 141 (13), 131 (6), 112 (24), 110 (4), 94 (10), 92 (9), 91 (100), 80 (4), 70 (5), 69 (7), 65 (4), 58 (11), 57 (29); exact mass calcd for $C_{26}H_{28}N_2O_7$ *m/e* 480.1897, obsd *m/e* 480.1886.

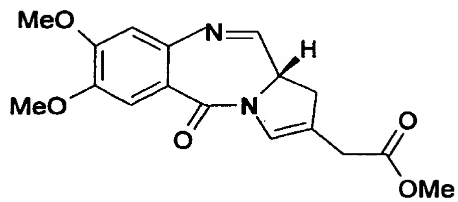
Example 1(d): (11a*S*)-8-Benzyloxy-2-(hydroxy-2-ethyl)-7-methoxy-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (33, UP2052, SJG-303).

A catalytic amount of tetrakis(triphenylphosphine)palladium (9.39 mg, 8.13 μmol) was added to a stirred solution of the Alloc-protected carbinolamine **30** (156 mg, 0.33 mmol), triphenylphosphine (4.26 mg, 16.3 μmol) and pyrrolidine (24.3 mg,

0.34 mmol) in CH_2Cl_2 (15 mL). After 1 h 50 min stirring at room temperature under a nitrogen atmosphere, TLC (90% $CHCl_3$/MeOH) revealed the complete consumption of starting material. The solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (98% $CHCl_3$/MeOH) to afford the PBD **(33, SJG-303, UP2052)** as an orange glass which was repeatedly evaporated *in vacuo* with $CHCl_3$ in order to provide the N10-C11 imine form (103 mg, 84%): ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.75 (d, 1H, J = 4.03 Hz), 7.58-7.22 (m, 6H), 6.82-6.80 (m, 2H), 5.17-4.88 (m, 2H), 4.65-4.20 (m, 2H), 3.91 (s, 3H), 3.35-3.25 (m, 1H), 3.18-3.15 (m, 1H), 3.04-2.97 (m, 1H), 2.52-2.47 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 162.8, 161.1, 152.3, 150.9, 148.1, 142.3, 138.3, 136.4, 128.7, 128.6, 128.2, 127.4, 124.2, 123.1, 111.8, 111.6, 70.8, 60.4, 56.2, 53.6, 37.7, 31.5; MS (EI), *m/z* (relative intensity) 380 (13), 379 (11), 378 ($M^{+\cdot}$, 42), 377 (36), 376 (77), 375 (6), 347 (8), 345 (5), 334 (5), 333 (19), 288 (14), 287 (14), 286 (36), 285 (50), 272 (6), 271 (22), 269 (6), 268 (6), 267 (5), 259 (5), 257 (13), 255 (24), 243 (15), 155 (6), 136 (5), 124 (7), 106 (6), 93 (6), 92 (38), 91 (100), 65 (16), 63 (5), 51 (5); IR ($CHCl_3$) 3313, 2918, 1623, 1598, 1568, 1509, 1455, 1436, 1386, 1328, 1243, 1218, 1175, 1130 1061, 1007, 870, 831, 792, 752, 697, 662 cm^{-1}; exact mass calculated for $C_{22}H_{22}N_2O_4$ m/e 378.1580, obsd m/e 378.1576.

Repeated evaporation *in vacuo* of **UP2052** with CH_3OH provided the N10-C11 methyl ether forms: ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.66-7.22 (m, 6H), 6.82-6.81 (m, 2H), 5.21-4.76 (m, 2H), 4.61-4.15 (m, 1H), 4.03-3.71 (m, 5H), 3.44 (s, 3H), 3.35-1.92 (m, 7H).

Example 1(e):Synthesis of the C7,C8-Dimethoxy-C2-Methoxycarbonylmethyl PBD AN-SJG (UP2065) (see Figure 4)



(2*S*)(4*R*)-*N*-(4,5-Dimethoxy-2-nitrobenzoyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (35)

A catalytic amount of DMF (2 drops) was added to a stirred solution of the nitro-acid **34** (12.45 g, 54.8 mmol) and oxalyl chloride (5.75 mL, 8.37 g, 65.9 mmol) in CH_2Cl_2 (300 mL). After 16 h at room temperature the resulting acid chloride solution was added dropwise over 4.5 h to a stirred mixture of the amine **2** (12.65 g, 54.8 mmol) and TEA (13.86 g, 19.1 mL, 137 mmol) in CH_2Cl_2 (300 mL) at 0°C (ice/acetone) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for a further 2.5 h. The mixture was washed with saturated $NaHCO_3$ (300 mL), saturated NH_4Cl (300 mL), H_2O (250 mL), brine (300 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude product as a dark orange oil. Purification by flash chromatography (80% EtOAc/Petroleum Ether) isolated the pure amide **35** as a sticky orange oil (18.11 g, 75%): $[\alpha]^{22}_D = -105.7°$ (c = 1.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.71 and 7.68 (s x 2, 1H), 6.86 and 6.79 (s x 2, 1H), 4.50 and 4.38 (br s x 2, 2H), 4.13-4.10 (m, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.78-3.74 (m, 1H), 3.35-3.27 (m, 1H), 3.07 (d, 1H, J = 11.17 Hz), 3.01-2.79 (br s, 1H), 2.35-2.26 (m, 1H), 2.11-

2.04 (m, 1H), 0.91 and 0.81 (s x 2, 9H), 0.10, 0.09, -0.07, and -0.10 (s x 4, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 166.6, 154.2 and 154.1, 149.3 and 148.9, 137.5, 128.0, 109.2, 107.1, 70.1 and 69.4, 64.7 and 62.5, 59.0 and 54.9, 57.3, 56.6, 56.5, 37.4 and 36.3, 25.9 and 25.7, 18.2, -5.4, -5.5 and -5.7; MS (EI), *m/z* (relative intensity) 440 ($M^{+\cdot}$, 2), 426 (9), 386 (4), 385 (20), 384 (65), 383 (100), 367 (4), 320 (4), 308 (7), 295 (8), 286 (5), 211 (15), 210 (100), 194 (12), 180 (4), 165 (17), 164 (8), 137 (4), 136 (25), 121 (4), 93 (6), 91 (9), 82 (6), 75 (15), 73 (15), 59 (4), 57 (4); IR (NEAT) 3391 (br, OH), 3012, 2952, 2931, 2857, 1616, 1578, 1522, 1456, 1436, 1388, 1338, 1279, 1225, 1183, 1151, 1074, 1053, 1029, 1004, 939, 870, 836, 816, 785, 757, 668, 650, 620 cm^{-1}; exact mass calcd for $C_{20}H_{32}N_2O_7Si$ *m/e* 440.1979, obsd *m/e* 440.1903.

(2*S*)(4*R*)-*N*-(2-Amino-4,5-dimethoxybenzoyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (36)

A solution of hydrazine (6.59 g, 6.40 mL, 205.5 mmol) in MeOH (110 mL) was added dropwise to a solution of the nitro-compound **35** (18.1 g, 41.1 mmol), over anti-bumping granules and Raney Ni (2.6 g) in MeOH (325 mL) and heated at reflux. After 1 h at reflux TLC (95% $CHCl_3$/MeOH) revealed some amine formation. The reaction mixture was treated with further Raney Ni (2.6 g) and hydrazine (6.40 mL) in MeOH (50 mL) and was heated at reflux for an additional 30 min at which point TLC revealed reaction completion. The reaction mixture was then treated with sufficient Raney Ni to decompose any remaining hydrazine and heated at reflux for a further 1.5 h. Following cooling to room

temperature the mixture was filtered through a sinter and the resulting filtrate evaporated *in vacuo*. The resulting residue was then treated with CH_2Cl_2 (300 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide the amine **36** as a green oil (16.03 g, 95%): $[\alpha]^{22}_D$ = −116.32 ° (*c* = 0.31, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 6.70 (s, 1H), 6.28 (s, 1H), 4.51-4.49 (m, 1H), 4.36-4.34 (m, 1H), 4.06-3.77 (m, 10H), 3.61-3.50 (m, 3H), 2.23-2.21 (m, 1H), 2.01-1.98 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 170.2, 151.5, 141.2, 140.5, 112.2, 112.0, 101.1, 70.4, 62.6, 59.0, 56.9, 56.6, 55.8, 35.7, 25.9 and 25.7, 18.2, −5.4 and −5.5; MS (EI), *m/z* (relative intensity) 412 ($M^{+\cdot}$ + 2, 3), 411 ($M^{+\cdot}$ + 1, 10), 410 ($M^{+\cdot}$, 32), 354 (6), 353 (23), 263 (3), 212 (5), 181 (11), 180 (100), 179 (3), 165 (3), 164 (6), 152 (10), 137 (4), 136 (4), 125 (5), 120 (3), 100 (3), 94 (6), 75 (9), 73 (7), 57 (3); IR ($CHCl_3$) 3353 (br), 2953, 2930, 2857, 1623, 1594, 1558, 1517, 1464, 1435, 1404, 1260, 1234, 1215, 1175, 1119, 1060, 1005, 915, 836, 777, 755, 666 cm^{-1}; exact mass calcd for $C_{20}H_{34}N_2O_5Si$ *m/e* 410.2237, obsd *m/e* 410.2281.

(2*S*)(4*R*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (37)

A solution of the amine **36** (16.03 g, 39 mmol) in CH_2Cl_2 (450 mL) was cooled to 0°C (ice/acetone) and treated with pyridine (6.94 mL, 6.78 g, 85.8 mmol). A solution of allyl chloroformate (4.35 mL, 4.94 g, 40.95 mmol) in CH_2Cl_2 (90 mL) was then added dropwise to the stirred mixture. The reaction mixture was allowed to warm to room temperature and stirred for a further 1.5 h, at which point TLC (EtOAc) revealed complete consumption of

amine **36**. The reaction mixture was washed with saturated $CuSO_4$ (300 mL), H_2O (300 mL), brine (300 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (35% EtOAc/Petroleum Ether) to afford the pure alloc-amino compound **37** as a clear oil (16.78 g, 87%): $[\alpha]^{23}_D = -93.35$ ° (c = 0.27, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 8.93 (br s, 1H), 7.72 (s, 1H), 6.77 (s, 1H), 6.01-5.87 (m, 1H), 5.34 (dd, 1H, J = 17.22, 3.12 Hz), 5.23 (dd, 1H, J = 10.44, 1.29 Hz), 4.63-4.55 (m, 3H), 4.40-4.38 (m, 1H), 4.15-4.08 (m, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.62-3.55 (m, 3H), 2.34-2.24 (m, 2H), 2.07-1.99 (m, 1H), 0.89 (s, 9H), 0.05 and 0.04 (s x 2, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 169.5, 153.8, 150.9, 143.8, 132.5, 118.0, 115.9, 111.0, 104.6, 70.5, 65.8, 62.2, 59.0, 57.2, 56.2, 56.0, 35.7 and 31.1, 25.8, 18.1, -5.4 and -5.5; MS (EI), m/z (relative intensity) 496 ($M^{+\cdot}$ + 2, 6), 495 ($M^{+\cdot}$ + 1, 18), 494 ($M^{+\cdot}$, 50), 439 (11), 438 (29), 437 (100), 380 (4), 379 (14), 337 (13), 336(4), 265 (15), 264 (91), 263 (4), 258 (6), 224 (4), 223 (15), 220 (11), 212 (7), 208 (4), 207 (11), 206 (75), 192 (5), 180 (20), 179 (18), 174 (15), 172 (4), 164 (7), 156 (5), 152 (5), 150 (6), 136 (4), 99 (9), 86 (16), 75 (10), 73 (11), 57 (6); IR ($CHCl_3$) 3337 (br), 2952, 2930, 2857, 1733, 1600, 1522, 1458, 1420, 1399, 1327, 1288, 1261, 1229, 1203, 1165, 1121, 1039, 1004, 931, 836, 777, 668 cm^{-1}; exact mass calcd for $C_{24}H_{38}N_2O_7Si$ m/e 494.2448, obsd m/e 494.2365.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-oxopyrrolidine (38)

A solution of DMSO (7.24 mL, 7.97 g, 102 mmol) in CH_2Cl_2 (150 mL)

was added dropwise over 2 h to a solution of oxalyl chloride (25.5 mL of a 2.0 M solution in CH_2Cl_2, 51.0 mmol) at −60°C (liq.N_2/$CHCl_3$) under a nitrogen atmosphere. After stirring at −50 °C for 1 h, a solution of the alcohol **37** (16.75 g, 33.9 mmol) in CH_2Cl_2 (250 mL) was added dropwise over a period of 2 h. After 1 h at −55°C, the mixture was treated dropwise with a solution of TEA (32.2 mL, 23.4 g, 231 mmol) in CH_2Cl_2 (100 mL) and allowed to warm to room temperature. The reaction mixture was treated with brine (250 mL) and washed with cold 1N HCl (2 X 300 mL). TLC (50% EtOAc/Petroleum Ether) analysis of the CH_2Cl_2 layer revealed complete reaction. The layers were separated and the organic phase washed with H_2O (300 mL), brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the ketone **38** as an orange glass (16.37 g, 98%): $[\alpha]^{21}_D$ = −9.96 ° (*c* = 1.51, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.82 (s, 1H), 6.75 (s, 1H), 6.01-5.89 (m, 1H), 5.36 (dd, 1H, *J* = 17.22, 3.11 Hz), 5.28-5.23 (m, 1H), 5.20-4.95 (m, 1H), 4.65-4.62 (m, 2H), 4.20-3.83 (m, 9H), 3.67-3.56 (m, 1H), 2.74 (dd, 1H, *J* = 17.86, 9.44 Hz), 2.52 (d, 1H, *J* = 17.95 Hz), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 208.9, 169.1, 153.5, 151.3, 143.9, 132.4, 118.2, 114.4, 110.1, 104.6, 66.1, 65.8, 56.2, 56.0, 39.7, 25.6, 18.0, −5.7 and −5.8; MS (EI), *m/z* (relative intensity) 494 ($M^{+\cdot}$ + 2, 6), 493 ($M^{+\cdot}$ + 1, 16), 492 ($M^{+\cdot}$, 43), 437 (8), 436 (22), 435 (74), 377 (11), 336 (6), 335 (21), 334 (8), 294 (8), 265 (9), 264 (50), 250 (5), 223 (17), 220 (18), 208 (7), 207 (15), 206 (100), 192 (9), 180 (23), 179 (28), 172 (33), 171 (10), 164 (16), 155 (7), 152 (9), 150 (16), 136 (13), 115 (14), 108 (6), 88 (6), 75 (20), 73 (33), 59 (13), 58

(6), 57 (62), 56 (14); IR (NEAT) 3337 (br, NH), 3086, 3019, 2954, 2932, 2858, 1766, 1732, 1623, 1603, 1520, 1464, 1398, 1362, 1332, 1313, 1287, 1262, 1204, 1166, 1110, 1052, 1038, 1004, 938, 870, 838, 810, 756, 666, 621, 600 cm^{-1}; exact mass calcd for $C_{24}H_{36}N_2O_7Si$ *m/e* 492.2292, obsd *m/e* 492.2349.

2*S*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (39)

Petroleum ether (70 mL) was added to a sample of NaH (0.41 g of a 60% dispersion in oil, 10.16 mmol) and stirred at room temperature under a nitrogen atmosphere. After 0.5 h the mixture was allowed to settle and the Petroleum Ether was transferred from the flask *via* a double-tipped needle under nitrogen. THF (60 mL) was added to the remaining residue and the mixture was cooled to 0°C (ice/acetone). The cool solution was treated dropwise with a solution of methyldiethylphosphonoacetate (1.86 mL, 2.14 g, 10.16 mmol) in THF (60 mL) under nitrogen. After 1.5 h at room temperature, the mixture was cooled to 0°C and treated dropwise with a solution of the ketone **38** (2.0 g, 4.07 mmol) in THF (36 mL) under nitrogen. After 16 h at room temperature, TLC (20% EtOAc/Petroleum Ether) revealed reaction completion. The THF was evaporated *in vacuo* and the mixture partitioned between saturated $NaHCO_3$ (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 X 100 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark red oil. Purification by

flash chromatography (15% EtOAc/Petroleum Ether) furnished the *endo*-ester **39** as a golden oil (1.63 g, 73%): ^{1}H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 8.82 (br s, 1H), 7.86 (s, 1H), 6.79 (s, 1H), 6.46 (br s, 1H), 6.03-5.89 (m, 1H), 5.39-5.32 (m, 1H), 5.24 (dd, 1H, J = 10.44, 1.28 Hz), 4.70-4.59 (m, 3H), 3.99-3.61 (m, 11H), 3.08 (s, 2H), 2.91-2.82 (m, 1H), 2.75-2.66 (m, 1H), 0.92-0.79 (m, 9H), 0.12--0.03 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 170.7, 165.8, 153.5, 151.3, 143.7, 132.8, 132.5, 128.2, 118.1, 118.0, 117.9, 111.3, 104.3, 65.7, 62.3, 59.5 and 59.4, 56.4, 56.0, 52.0, 34.7, 33.9, 25.8, 18.1, -5.4; MS (EI), *m/z* (relative intensity) 549 ($M^{+\cdot}$ + 1, 7), 548 ($M^{+\cdot}$, 17), 525 (13), 507 (14), 492 (6), 491 (18), 489 (8), 449 (7), 347 (11), 287 (6), 286 (20), 285 (82), 265 (10), 264 (51), 263 (9), 244 (9), 242 (7), 228 (19), 227 (8), 226 (18), 224 (6), 223 (22), 220 (12), 208 (6), 207 (18), 206 (100), 192 (7), 180 (18), 179 (21), 168 (16), 164 (10), 152 (13), 150 (8), 141 (8), 140 (73), 139 (13), 136 (6), 108 (6), 89 (9), 80 (15), 75 (15), 73 (19), 57 (6); exact mass calcd for $C_{27}H_{40}N_2O_8Si$ *m/e* 548.2554, obsd *m/e* 548.2560

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(hydroxymethyl)-4-(methoxycarbonylmethyl)-2,3-dihydropyrrole (40). A solution of the silyl ether **39** (1.63 g, 2.97 mmol) in THF (12.6 mL) was treated with H_2O (12.6 mL) and glacial acetic acid (38 mL). After 2 h stirring at room temperature TLC (60% EtOAc/Petroleum Ether) showed the complete consumption of starting material. The mixture was cooled (ice) and treated dropwise with a solution of $NaHCO_3$ (61.6 g) in H_2O (616 mL). The aqueous solution was extracted with EtOAc (3 X 150 mL) and the

combined organic layers were washed with H_2O (150 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude alcohol **40** as an orange oil (1.27 g, 98%): MS (EI), *m/z* (relative intensity) 435 ($M^{+\cdot}$ + 1, 6), 434 ($M^{+\cdot}$, 23), 347 (5), 317 (4), 281 (6), 265 (8), 264 (44), 263 (8), 224 (5), 223 (24), 222 (5), 220 (9) 207 (15), 206 (94), 192 (5), 180 (18), 179 (18), 172 (12), 171 (100), 164 (12), 152 (7), 150 (7), 141 (6), 140 (53), 136 (9), 112 (11), 108 (6), 80 (12), 69 (7); exact mass calcd for $C_{21}H_{26}N_2O_8$ *m/e* 434.1689, obsd *m/e* 434.1606.

(11*S*,11a*S*)-10-Allyloxycarbonyl-7,8-dimethoxy-11-hydroxy-2-(methoxycarbonylmethyl)-1,10,11,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (41)

A solution of DMSO (0.75 mL, 0.82 g, 10.5 mmol) in CH_2Cl_2 (22 mL) was added dropwise over 1 h 20 min to a solution of oxalyl chloride (2.63 mL of a 2.0 M solution in CH_2Cl_2, 5.26 mmol) at -45 °C (liq.N_2/Chlorobenzene) under a nitrogen atmosphere. After stirring at -45°C for 1 h, a solution of the alcohol **40** (1.27 g, 2.92 mmol) in CH_2Cl_2 (22 mL) was added dropwise over 1 h at -45°C. After 50 min at -45°C, the mixture was treated dropwise with a solution of TEA (1.71 mL, 1.24 g, 12.29 mmol) in CH_2Cl_2 (11 mL) over 30 min at -45°C. After a further 30 min, the reaction mixture was allowed to warm to room temperature and was diluted with CH_2Cl_2 (20 mL), washed with 1N HCl (100 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. TLC (80% EtOAc/Petroleum Ether) of the crude material revealed reaction completion. Purification by flash chromatography (55% EtOAc/Petroleum Ether) furnished the

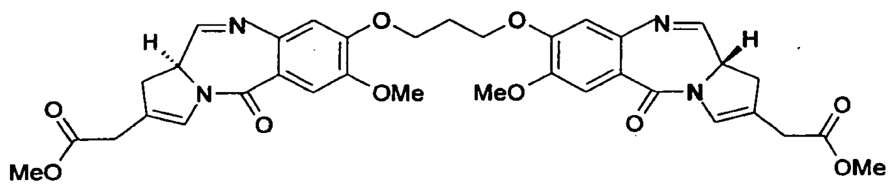
protected carbinolamine **41** as a white glass (0.68 g, 54%): $[\alpha]^{22}_D$ = +219.78 ° (c = 0.12, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.91 (s, 1H), 6.70 (s, 1H), 5.90-5.80 (m, 2H), 5.17-5.13 (m, 2H), 4.70 (dd, 1H, J = 13.37, 5.31 Hz), 4.50-4.43 (m, 1H), 3.98-3.75 (m, 8H), 3.71 (s, 3H), 3.20-3.05 (m, 3H), 2.75 (d, 1H, J = 17.04 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.7, 163.3, 155.9, 151.1, 148.5, 131.7, 128.3, 126.2, 124.7, 118.1, 117.6, 112.6, 110.6, 86.0, 66.8, 59.4, 56.2, 52.1, 37.0, 33.7; MS (EI), m/z (relative intensity) 434 ($M^{+\cdot}$ + 2, 6), 433 ($M^{+\cdot}$ + 1, 21), 432 ($M^{+\cdot}$, 74), 414 (8), 373 (14), 329 (7), 293 (20), 292 (20), 265 (19), 264 (100), 263 (33), 248 (25), 224 (6), 223 (25), 220 (14), 209 (8), 208 (52), 207 (24), 206 (92), 192 (15), 191 (6), 190 (7), 180 (18), 179 (23), 169 (23), 165 (10), 164 (17), 152 (12), 150 (14), 149 (8), 141 (9), 140 (60), 136 (11), 125 (6), 120 (5), 110 (8), 108 (15), 81 (9), 80 (45), 57 (7); IR ($CHCl_3$) 3385 (br), 2918, 2849, 1707, 1625, 1605, 1516, 1457, 1436, 1405, 1311, 1282, 1245, 1217, 1172, 1116, 1046, 1001, 968, 933, 874, 855, 666 cm^{-1}.

(11a*S*)-7,8-Dimethoxy-2-(methoxycarbonylmethyl)-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (42, UP2065, AN-SJG)

A catalytic amount of tetrakis(triphenylphosphine)palladium (44.0 mg, 38.0 μmol) was added to a stirred solution of the Alloc-protected carbinolamine **41** (0.66 g, 1.53 mmol), triphenylphosphine (20.0 mg, 77.0 μmol) and pyrrolidine (114 mg, 1.60 mmol) in CH_2Cl_2 (100 mL). After 2 h stirring at room temperature under a nitrogen atmosphere, TLC (99% $CHCl_3$/MeOH) revealed the complete consumption of starting material. The

solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (98% $CHCl_3$/MeOH) to afford the PBD **(42, AN-SJG, UP2065)** as an orange glass which was repeatedly evaporated *in vacuo* with $CHCl_3$ in order to provide the N10-C11 imine form (481 mg, 95%): $[\alpha]^{22}_D = +401.84°$ (c = 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1H), 7.49 (s, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 4.34-4.27 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.74 (s, 3H), 3.34 (d, 1H, J = 16.85 Hz), 3.24 (s, 2H), 3.19-3.10 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.6, 162.7, 161.4, 151.8, 147.7, 140.4, 126.5, 119.0, 117.4, 111.5, 109.8, 56.2, 56.1, 53.8, 52.1, 37.4, 33.6; MS (EI), m/z (relative intensity) 332 ($M^{+\cdot}$ + 2, 5), 331 ($M^{+\cdot}$ + 1, 9), 330 ($M^{+\cdot}$, 41), 329 (28), 328 (100), 313 (18), 272 (8), 271 (24), 270 (14), 269 (27), 262 (7), 257 (12), 255 (5), 242 (6), 225 (7), 197 (4), 192 (16), 191 (16), 183 (6), 164 (14), 136 (11), 135 (9), 106 (9), 80 (17), 53 (5); IR ($CHCl_3$) 3329 (br), 3112, 2952, 2842, 1737, 1626, 1602, 1512, 1453, 1436, 1381, 1356, 1246, 1213, 1173, 1096, 1069, 1008, 875, 840, 786, 666, 620, 574, 537 cm^{-1}; exact mass calcd for $C_{17}H_{18}N_2O_5$ m/e 330.1216, obsd m/e 330.1237.

Example 1(f): Synthesis of KEC-570 (115, UP-2053) (see Figure 5)



1′, 3′-Bis(4-carboxy-2-methoxyphenoxy)propane (43)

A solution of diiodopropane (8.79 g, 29.7 mmol) in THF (50 mL), was added dropwise over a period of 4 h to a vigorously stirred solution of vanillic acid (10 g, 59.5 mmol) in THF (100 mL) and aqueous NaOH (225 mL, 0.5 M) at 65°C in the absence of light (foil-wrapped flask). After heating at reflux for 48 h in the dark, the suspension was cooled, washed with hexane (3 x 100 mL) and the THF removed by evaporation *in vacuo*. The aqueous residue was acidified to pH 1 with conc. HCl and the resultant precipitate collected by filtration, dried and recrystallised from glacial acetic acid to afford the corresponding bis-carboxylic acid (**118**) as a white crystalline solid (9.4g, 84%). mp 238-240°C; ^{1}H-NMR (DMSO-d_6): δ 2.23 (t, 2H, J = 6.0 Hz, **H13**), 3.80 (s, 6H, **CH_3O**), 4.20 (t, 4H, J = 6.0 Hz, **H12**), 7.09 (d, 2H, J = 8.4 Hz, **H10**), 7.45 (d, 2H, J = 1.8 Hz, **H6**) 7.54 (dd, 2H, J = 8.4 Hz, 1.8 Hz, **H9**), 12.76 (bs, 2H, **CO_2H**); ^{13}C-NMR (DMSO-d_6) δ 28.4 (**C13**), 55.4 (**CH_3O**), 64.8 (**C12**), 111.9 (**C9**), 112.0 (**C6**), 122.9 (**C10**), 123.0 (**Q**), 148.3 (**Q**), 151.6 (**Q**), 167.0 (**C=O**). IR (KBr): ν = 3600-2000, 1680 (C=O), 1600 (C=C), 1515, 1465, 1430, 1345, 1310, 1270, 1225 (C-O-C), 1180, 1140, 1115, 1030, 990, 970, 950, 925, 875, 850, 825, 765, 725, 645 cm^{-1}. MS (EI): *m/z* (relative intensity) 376 ($M^{+\cdot}$, 28), 360 (3), 249 (2), 209 (45), 165 (29), 153 (16), 151 (19), 137 (19), 121 (7), 78 (15), 44 (100); HRMS: Calcd for $C_{19}H_{20}O_8$ = 376.1158 found 376.1168.

1′,3′-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (44)

The diacid **43** (2.0 g, 5.30 mmol) was added portionwise to conc. HNO_3 (40 mL) at -10°C and stirred to room temperature over 12 h. The reaction mixture was poured on to ice (400 mL) and the resulting precipitate collected by filtration, washed with ether (3 x 50 mL) and dried to afford the nitro acid (**121**) as a yellow solid (1.73 g, 70%). m.p. 243-246°C. ^{1}H-NMR (DMSO-d_6): δ 2.25 (t, 2H, J = 5.9 Hz, **H13**), 3.90 (s, 6H, **CH_3O**), 4.27 (t, 4H, J = 5.9 Hz, **H12**), 7.29 (s, 2H, **H6**), 7.62 (s, 2H, **H9**), 13.6 (bs, 2H, **CO_2H**). ^{13}C-NMR (DMSO-d_6) δ 28.0 (**C13**), 56.3 (**CH_3O**), 65.7 (**C12**), 108.0 (**C9**), 111.2 (**C6**), 121.1 (**C5**), 141.3 (**Q**), 149.1 (**C8**), 151.7 (**Q**), 165.9 (**C=O**). IR (KBr): ν = 3620-2280, 1700 (C=O), 1595 (C=C), 1570, 1515 (NO_2), 1460, 1415, 1350 (NO_2), 1270, 1210, 1180, 1135, 1045, 930, 880, 810, 750, 730, 645 cm^{-1}. MS (EI): m/z (relative intensity) 467 ($MH^{+\cdot}$, 1), 450 (1), 436 (3), 423 (8), 378 (4), 268 (1), 255 (4), 236 (4), 210 (7), 194 (2), 182 (7), 164 (14), 153 (2), 123 (3), 91 (6), 77 (3), 55 (5), 44 (100). HRMS (EI) m/z calcd for $C_{19}H_{18}N_2O_{12}$ = 466.0860 found 466.0871.

(2*S*,4*R*)-*N*-(Benzoxycarbonyl)-2-carboxy-4-hydroxypyrrolidine (45)

A solution of benzyl chloroformate (12.5 mL, 87.7 mL) in toluene (40 mL) was added to a solution of *trans*-4-hydroxy-L-proline **11** (10 g, 76.3 mmol) and $NaHCO_3$ (16 g, 190 mmol) in H_2O (165 mL) over a period of 15 min. After stirring at room temperature for 12 h the two phases were allowed to separate. The aqueous phase was washed with diethyl ether (4 x 50 mL), cooled in an ice bath,

and then acidified to pH 2 with conc. HCl. The resultant product was extracted with ethyl acetate (5 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and the excess solvent evaporated *in vacuo* to afford a colourless viscous oil (20.30 g, 100%). $[\alpha]^{27}_D = -565°$ (*c* 0.1, MeOH). ^1H NMR ($CDCl_3$): δ 2.07-2.31 (m, 3H, **H1**), 3.52-3.59 (m, 2H, **H3**), 4.43-4.53 (m, 2H, **H2**, **H11a**), 5.8 and 5.11 (s, 2H, minor and major rotamers of **H6**, 1:2), 6.0 (bs, 2H, **OH**), 7.26-7.29 and 7.32-7.34 (m, 5H, minor and major rotamers of **H arom**, 1:2). IR (thin film): ν = 3414 (OH), 2940 (OH), 1682 (C=O), 1495, 1429, 1359 (CO_2^-), 1314, 1269, 1205, 1180, 1174, 1127, 1082, 1051, 993, 914, 866, 826, 769, 741, 697 cm^{-1}. MS (EI): m/e (relative intensity): 266 ($M^{+\cdot}$, 1), 265 (6), 220 (5), 176 (15), 130 (34), 108 (2). 91 (100), 86 (4), 68 (11). HRMS calcd. for $C_{13}H_{15}NO_5$ = 265.0950 found 265.0976

(2*S*,4*R*)-*N*-(Benzoxycarbonyl)-2-methyoxycarbonyl-4-hydroxyproline (46)

A solution of (2*S*,4*R*)-*N*-(Benzoxycarbonyl)-2-carboxy-4-hydroxypyrrolidine (**45**) (20.30 g, 76.3 mmol) in dry methanol (300 mL) was heated at reflux for 18 h in the presence of a catalytic amount of conc. H_2SO_4 (2.20 mL, 7.63 mmol). The reaction mixture was allowed to cool to room temperature and neutralised with Et_3N (3.0 mL, 76.3 mmol). The reaction mixture was concentrated *in vacuo* and the residue redissolved in ethyl acetate (200 mL), washed with brine (1 x 50 mL), dried ($MgSO_4$) and excess solvent removed under reduced pressure to afford a colourless gum (21.17 g, 99%). $[\alpha]^{20}_D = -59.4°$ (*c* 0.014, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 2.04-2.08 and 2.24-2.35(m, 1H, rotamers of **H1**,

1:1), 2.64 (bs, 1H, **OH**), 3.54 and 3.74 (s, 3H, rotamers of **OMe**, 1:1), 3.66-3.69 (m, 2H, **H3**), 4.47-4.50 (m, 2H, **H2**, **H11a**), 5.07-5.13 (m, 2H, **H6**), 7.26-7.35 (m, 5H, **H arom**). ^{13}C NMR ($CDCl_3$): rotamer ratio 1:1, δ 37.8 and 38.5 rotamers of (**C1**), 51.8 and 52.0 rotamers of (**OMe**), 54.1 and 54.7 rotamers of (**C3**), 57.4 and 57.7 rotamers of (**C2**), 66.9 and 67.0 rotamers of (**C6**), 68.6 and 69.3 rotamers of (**C11a**), 127.0, 127.3, 127.4, 127.7, 127.8, 128.0 and 128.1 rotamers of (**C arom**). IR (thin film): ν = 3435 (OH), 3033, 2953 (OH), 1750 (ester), 1680 (C=O), 1586, 1542, 1498, 1422, 1357 (CO_2H), 1170, 1124, 1084, 1052 (C-O), 1004, 963, 916, 823, 770, 750, 699, 673 cm^{-1}. MS (FAB) m/z (relative intensity): 280 ($M^{+\cdot}$, 24), 236 (20), 234 (4), 216 (8), 214 (4), 213 (2), 206 (2), 204 (7), 203 (4), 202 (10), 201 (2), 181 (5), 144 (16), 102 (23), 91 (100). HRMS calcd. for $C_{14}H_{17}NO_5$ = 279.1107 found 279.1192

(2*S*,4*R*)-*N*-(Benzoxycarbonyl)-2-hydroxymethyl-4-hydroxyproline (47)

Lithium borohydride (1.57 g, 73 mmol) was added portionwise to a solution of (2*S*,4*R*)-*N*-(benzoxycarbonyl)-2-methyoxycarbonyl-4-hydroxyproline (**46**) (20.17 g, 73 mmol) in THF (350 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stir overnight. The resulting suspension was cooled to 0°C and quenched with water (2-3 mL) until effervescence ceased, at which point 2 M HCl (15 mL) was added to dissolve the precipitate. The product was extracted with ethyl acetate (3 x 150 mL) and the combined organic phases washed with brine (1 x 100 mL) and then dried ($MgSO_4$). Concentration *in vacuo* afforded a white gum (18.25 g, 100%). $[\alpha]^{22.3}_D = -404°$ (C = 0.043, $CHCl_3$). ^{1}H NMR

($CDCl_3$): δ 1.24-1.26 (m, 1H, **H1**), 1.73-2.08 (m, 1H, **H1**), 3.40-4.30 (m, 6H, **H2**, **H3**, **H11**, **H11a**), 5.06 (bs, 1H, **OH**), 5.09 (s, 2H, **H6)** 7.25-7.31 (m, 5H, **H arom**). ^{13}C NMR ($CDCl_3$): δ 36.7 (**C1**), 55.2 (**C3**), 58.7 (**C2**), 65.0 (**C11**), 67.0 (**C6**), 68.7 (**C11a**), 127.0, 127.5 (**C arom**), 127.8 (**C arom**), 128.2 (**C arom**). IR (thin film): ν = 3390 (OH), 3065, 3033, 2953 (OH), 1681 (C=O carbamate), 1586, 1538, 1498, 1454, 1192, 1122, 978, 914, 862, 770, 698, 673 cm^{-1}. MS (FAB) m/z (relative intensity): 252 ($M^{+\cdot}$, 58), 208 (33), 176 (5), 144 (6), 118 (8), 116 (7), 92 (13), 91 (100). HRMS calcd. for $C_{13}H_{17}NO_4$ = 251.1158 found 251.1230.

(2*S*,4*R*)-*N*-Benzoxycarbonyl-2-*t*-butyldimethylsilyloxymethyl-4-hydroxypyrrolidine (48)

t-butyldimethylsilyl chloride (5.78 g, 38.3 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.44 mL, 9.6 mmol) were added to a solution of alcohol (**47**) (12.51 g, 49.8 mmol) and triethylamine (7.0 mL, 49.8 mmol) in dry DCM (200 mL) which had been allowed to stir for 15 min at room temperature. The resulting mixture was allowed to stir at room temperature for 18 h and then diluted with ethyl acetate (300 mL). The organic phase was washed with aqueous saturated ammonium chloride (2 x 100 mL) and brine (1 x 100 mL) dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a colourless viscous oil (9.84 g, 70%). $[\alpha]^{22.3}_D$ = -263° (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$) : δ -0.05 and -0.06(s, 6H, rotamers of **H1′**, **H2′**, 1:1), 0.83 and 0.85 (s, 9H, rotamers of **H3′**, **H5′**, **H6′**, 1:1), 1.95-2.22 (m, 2H, **H1**,), 2.78 (bs, 1H, **OH**), 3.44-3.68 (m, 3H, **H3**, **H11**), 3.99-4.10 (m, 1H, **H2**), 4.43-4.46 (m, 1H, **H11a**), 5.11-5.16 (m, 2H, **H6)** 7.34-7.35 (m, 5H,

H arom) ^{13}C NMR ($CDCl_3$): rotamer ratio of 1:1, δ -5.50 (**C3′, C5′, C6′**), 18.15 (**C4′**), 25.83 (**C1′, C2′**), 36.55 and 37.27 rotamers of (**C1**), 55.2 and 55.7 rotamers of (**C3**), 57.3 and 57.8 rotamers of (**C2**), 62.8 and 63.9 rotamers of (**C11**), 66.6 and 67.0 rotamers of (**C6**), 69.7 and 70.3 rotamers of (**C11a**), 127.8 (**C arom**), 127.9 (**C arom**), 128.0 (**C arom**), 128.4 (**C arom**), 128.5 (**C arom**), 136.5 and 136.8 rotamers of (**C7**), 154.9 and 155.2 rotamers of (**C5**). IR (thin film): ν = 3415 (OH), 3066, 3034, 2953 (OH), 2930, 2884, 2857, 1703 (C=O carbamate), 1587, 1498, 1424, 1360 ($C-CH_3$), 1288 (CH_3Si), 1255 (*t*-Bu), 1220, 1195 (*t*-Bu), 1118 (Si-O), 1057, 1003, 917, 836, 774, 751, 698, 670 cm^{-1}. MS (EI/CI) m/e (relative intensity): 366 ($M^{+\cdot}$, 100), 308 (14), 258 (2), 91 (2).

(2*S*,4*R*)-2-*t*-butyldimethylsilyloxymethyl-4-hydroxypyrrolidine (2)

A slurry of 10% Pd/C (190 mg) in ethyl acetate (20 mL) was added to a solution of TBDMS ether (**48**) (1.90 g, 5.19 mmol) in ethanol (100 mL). The reaction mixture was hydrogenated (Parr apparatus) for 16 h. The catalyst was removed by vacuum filtration through Celite and excess solvent was evaporated under reduced pressure to give a yellow oil in quantitative yield (1.20 g, 100%). $[\alpha]^{22.2}{}_{D}$ = +35.6° (*c* 0.042, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ -(0.07-0.08) (m, 6H, **H1′, H2′**), 0.82 (s, 9H, **H3′, H4′, H5′**), 1.68-1.73 (m, 2H, **H1**,), 2.99-3.11 (m, 2H, **H11**), 3.47-3.50 (m, 3H, **H11a, H3**), 4.09 (bs, 1H, **NH or OH**), 4.32 (bs, 1H, **NH or OH**). ^{13}C NMR ($CDCl_3$): δ -5.4 (**C3′, C5′, C6′**), 18.1 (**C4′**), 25.8 (**C1′, C2′**), 37.4 (**C1**), 54.6 (**C11**), 58.1 (**C2**), 64.6 (**C3**), 72.2 (**C11a**). IR (thin film): ν = 3330 (OH), 2928, 2857, 1557, 1421, 1331 ($C-CH_3$), 1249 (CH_3-Si),

1204 (*t*-Bu), 1191 (*t*-Bu), 1100 (Si-O),1073, 993, 713 cm^{-1}. MS (CI) m/e (relative intensity): 232 ($M^{+\cdot}$, 100), 230 (13), 174 (5), 133 (6), 86 (6).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-nitro-5-methoxy-1,4-phenylene)carbonyl]]-bis[(2*S*,4*R*)-2-*t*-butyldimethylsilyloxymethyl-4-hydroxypyrrolidine (49)

A catalytic amount of DMF (2 drops) was added to a stirred suspension of bis-nitroacid (**44**) (2.00 g, 4.28 mmol) and oxalyl chloride (0.94 mL, 10.70 mmol) in dry THF (20 mL), and the reaction mixture was allowed to stir for 4 h. After evaporation of excess THF *in vacuo*, the resultant yellow residue was dissolved in dry THF (20 mL) and added dropwise over a period of 25 min to a vigorously stirred suspension of amine (**2**) (2.47 g, 10.70 mmol), Et_3N (2.50 mL, 17.9 mmol) and ice/water (0.6 mL) cooled in an ice bath. The mixture was then allowed to warm to room temperature for a further 1.5 h. After removal of the THF by evaporation *in vacuo,* the residue was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with water (3 x 25 mL) and brine (3 x 25 mL), dried ($MgSO_4$), and the solvent removed *in vacuo* to afford a yellow oil which was purified by flash chromatography (3% MeOH/$CHCl_3$) to afford the bis-amide (**49**) as a yellow solid (2.05g, 54%). $[\alpha]^{23.8}{}_D = -993°$ (*c* 0.033, $CHCl_3$). ^1H NMR ($CDCl_3$): δ -0.05 (s, 12H, **H1′**, **H2′**), 0.80 (s, 18H, **H3′**, **H5′**, **H6′**), 1.96-1.99 (m, 2H, **H1**), 2.14-2.16(m, 2H, **H1**), 2.19-2.24 (m, 2H, **H13**), 2.85-2.89 (m, 2H, **H2**) 3.16-3.19 (m, 4H, **H11**), 3.63-3.66 (m, 4H, **H3**), 3.81 (s, 6H, **OMe**), 3.99-4.10 (m, 2H, **H3**), 4.23

(t, 4H, J = 5.3 Hz, **H12**), 4.38 (bs, 2H, **OH**); 5.20-5.25 (m, 2H, **H11a**), 6.65 (s, 2H, **H6**), 7.55 (s, 2H, **H9**). ^{13}C-NMR ($CDCl_3$): δ -5.35 (**C1′**, **C2′**), 18.2 (**C4′**), 25.8 (**C3′**, **C5′**, **C6′**), 28.9 (**C13**), 36.1 (**C1**), 54.9 (**CH_3O**), 56.6 (**C4**), 57.3 (**C12**), 65.0 (**C3**), 70.0 (**C2**), 108.0 (**C6**), 109.4 (**C9**), 128.2 (**Q**), 137.2 (**Q**), 148.1 (**Q**), 148.5 (**Q**), 154.5 (**Q**), 166.5 (**Q**). IR (thin film): ν = 3392 (OH), 2950, 2856, 1623 (C=O), 1577 (C arom), 1524 (NO_2), 1459, 1432, 1381, 1338 (C-CH_3), 1278 (CH_3-Si), 1219 (t-Bu), 1184 (t-Bu), 1075 1053, 1004, 938, 914, 837, 778, 724, 668, 649, cm^{-1}. MS (FAB) m/z (relative intensity) : 894 ($M^{+\cdot}$, 8), 893 (19), 878 (6), 835 (2), 779 (9), 761 (6), 517 (3), 459 (5), 258 (7), 100 (3), 86 (4), 75 (29), 73 (100), 59 (17), 58 (6).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-amino-5-methoxy-1,4-phenylene)carbonyl]]-bis[(2*S*,4*R*)-2-*t*-butyldimethylsilyloxymethyl-4-hydroxypyrrolidine (50)

A slurry of 10% Pd/C (155 mg) in ethyl acetate (20 mL) was added to a solution of the bis-amide (**49**) (1.55 g, 1.73 mmol) in ethanol (100 mL). The reaction mixture was hydrogenated (Parr apparatus) for 16 h. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to give a yellow oil (**50**) in quantitative yield (1.44 g, 100%). ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 12H, **H1′**, **H2′**), 0.88 (s, 18H, **H3′**, **H5′**, **H6′**), 2.00-2.25 (m, 6H, **H1**, **H13**), 3.50-3.72 (m, 12H, **H2**, **H3**, **H11**, **H11a**), 3.74 (s, 6H, **OMe**), 4.16-4.20 (m, 4H, **H3**), 4.30-4.35 (m, 4H, **H12**), 4.49 (bs, 2H, **OH**); 6.23 (s, 2H, **H9**), 6.64 (s, 2H, **H6**) ^{13}C-NMR ($CDCl_3$): δ -5.5 (**C1′**, **C2′**), 18.1 (**C4′**), 25.8 (**C3′**, **C5′**, **C6′**), 29.6 (**C13**), 35.2 (**C1**), 56.7 (**CH_3O**), 62.2 (**C4**), 64.1 (**C3**),

70.0 (**C2**), 102.2 (**C9**), 112.6 (**C6**), 140.4 (**Q**), 141.1 (**Q**), 150.6 (**Q**), 170.1 (**Q**); IR (neat): ν = 3359 (OH), 2929, 2856, 1621 (C=O), 1591 (C arom), 1469, 1433, 1406, 1358, 1346 ($C-CH_3$), 1261 (CH_3-Si), 1232 (*t*-Bu), 1175 (*t*-Bu), 1117, 1056, 1006, 866, 835, 776 cm^{-1}. MS (FAB) m/z (relative intensity) : 834 ($M^{+\cdot}$, 13), 833 (18), 773 (9), 602 (13), 399 (7), 371 (34), 232 (9), 206 (22), 192 (14), 176 (13), 166 (44), 150 (8), 100 (10), 73 (100).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-amino-*N*-allyloxycarbonyl-5-methoxy-1,4-phenyl-ene)-carbonyl]]-bis[(2*S*,4*R*)-2-t-butyldimethylsilyloxymethyl-4-hydroxy-pyrrolidine (51)

A solution of the bis-amide (**50**) (2.76 g, 3.31 mmol) and pyridine (1.10 mL, 13.60 mmol) in dried DCM (100 mL) was cooled to 0°C. Allyl chloroformate (0.80 mL, 7.53 mmol) in DCM (50 mL) was added dropwise and the resulting mixture allowed to warm to room temperature and stirred for 16h. The reaction mixture was diluted with DCM (200 mL) and washed with 1 M $CuSO_4$ (3 x 50 mL), water (1 x 50 mL) and brine (1 x 50 mL) before drying ($MgSO_4$). Evaporation of the solvent under reduced pressure followed by flash column chromatography (2.5% MeOH/DCM) afforded (**51**) as a yellow solid (3.24 g, 97%). $[\alpha]^{20.1}{}_D = -571°$ (*c* 0.007, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.00 (s, 12H, **H1′**, **H2′**), 0.89 (s, 18H, **H3′**, **H5′**, **H6′**), 2.03-2.36 (m, 6H, **H1**, **H13**), 3.51-3.58 (m, 6H, **H2**, **H3**), 3.77 (s, 6H, **OMe**), 4.20-4.26 (m, 8H, **H11**, **H12**), 4.28-4.30 (m, 2H, **H11a**), 4.56-4.60 (m, 6H, **H8′**, **OH**), 5.25 (dd, $J_{1,2}$= 1.5 Hz, $J_{1,3}$ = 15.0 Hz, 4H, **H10′**), 5.90-5.95 (m, 2H, **H9′**), 6.73 (s, 2H, **H6**), 7.63 (s, 2H, **H9**), 8.80 (s, 2H, **NH**). ^{13}C NMR ($CDCl_3$): δ -5.42 (**C1′**, **C2′**), 25.8 (**C3′**, **C5′**, **C6′**), 29.2 (**C13**), 35.4 (**C1**), 56.3

(CH_3O), 57.1 (**C11a**), 59.8 (**C11**), 62.2 (**C3**), 65.1 (**C12**), 65.7 (**C8′**), 70.5 (**C2**), 106.3 (**C9**), 111.5 (**C6**), 116.5 (**Q**), 118.1 (**C10′**), 131.7 (**Q**), 132.5 (**C9′**), 144.3 (**Q**), 150.3 (**Q**), 153.8 (**Q**), 169.5 (**Q**). IR (neat): ν = 3351 (OH), 2931, 2857, 1762 (Alloc C=O), 1722, 1603 (C=O), 1521 (C arom), 1463, 1404, 1264 (CH_3-Si), 1222 (*t*-Bu), 1106 (*t*-Bu), 1053, 1015, 936, 872, 837, 775, 629, cm^{-1}.

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-amino-*N*-allyloxycarbonyl-5-methoxy-1,4-phenylene)-carbonyl]]-bis[(2*S*)-2-*t*-butyldimethylsilyloxymethyl-4-oxo-pyrrolidine (52)

A solution of dimethyl sulphoxide (2.10 mL, 28.5 mmol) in dry DCM (20 mL) was added dropwise over a 15 min period to a stirred, cooled (-45°C) solution of oxalyl chloride (1.27 mL, 14.60 mmol) in DCM (30 mL). After 35 min, a solution of alcohol (**51**) (2.54g, 2.53 mmol) in DCM (20 mL) was added dropwise over a period of 15 min to the reaction mixture at -45°C. After 45 min a solution of triethylamine (5.75 mL, 40.3 mmol) in DCM (20 mL) was added over a period of 15 min and the reaction mixture stirred at -45°C for 30 min before warming to room temperature over 45 min. The mixture was then washed with 1 M $CuSO_4$ (3 x 50 mL), water (2 x 50 mL) and brine (1 x 50 mL) before drying ($MgSO_4$) and concentrating *in vacuo* to give (**52**) as a yellow solid (2.46g, 97%). ^1H NMR ($CDCl_3$): δ 0.00 (s, 12H, **H1′**, **H2′**), 0.86 (s, 18H, **H3′**, **H5′**, **H6′**), 2.50 -2.63 (m, 6H, **H1**, **H13**), 3.63-3.70 (m, 4H, **H3**), 3.80 (s, 6H, **OMe**), 3.93-3.97 (m, 6H, **H11**, **H11a**), 4.29-4.32 (m, 4H, **H12**), 4.62 (d, 4H, *J* = 5.7 Hz, **H8′**), 5.27-5.32 (m, 4H, **H10′**), 5.98-6.03 (m, 2H, **H9′**), 6.74 (s, 2H, **H6**), 7.74 (s, 2H,

H9), 8.80 (s, 2H, **NH**). ^{13}C NMR ($CDCl_3$): δ -5.76 (**C1′**, **C2′**), 18.0 (**C4′**), 25.7 (**C3′**, **C5′**, **C6′**), 28.8 (**C13**), 39.6 (**C1**), 55.0 (**C3**), 56.4 (**CH_3O**), 65.3 (**C12**), 65.8 (**C8′**), 105.9 (**C9**), 110.7 (**C6**), 118.2 (**C10′**), 132.4 (**C9′**), 150.7 (**Q**), 153.5 (**Q**), 169.1 (**Q**), 210.0 (**C2**). IR (neat): ν = 3308 (OH), 2931, 2856, 1765 (Alloc C=O), 1730, 1624 (C=O), 1602 (C=O), 1522 (C arom), 1468, 1407, 1332, 1259 (CH_3-Si), 1204 (*t*-Bu), 1105 (*t*-Bu), 1053, 1010, 937, 870, 837, 808, 778, 674, 657 cm^{-1}.

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-amino-*N*-allyloxycarbonyl-5-methoxy-1,4-phenylene)-carbonyl]]-bis[(2*S*)-2-t-butyldimethylsilyloxymethyl-4-methoxycarbonyl methyl-2,3-dihydropyrrole (53)

A solution of diethylmethylphosphonoacetate (0.80 mL, 4.21 mmol) in THF (50 mL) was added to a suspension of NaH (343 mg, 4.21 mmol, 60% dispersion in mineral oil, washed with petroleum ether) in dry THF (50 mL) at 0°C under a nitrogen atmosphere. After stirring at room temperature for 1 h, a solution of the dimer ketone (**52**) (2.04 g, 2.00 mmol) in THF (50 mL) was added dropwise at 0°C. The reaction mixture was allowed to warm to room temperature over 18 h. Excess THF was removed under reduced pressure and the residue cooled in an ice bath before adding $NaHCO_3$ (50 mL) followed by EtOAc (50 mL). The layers were separated and the aqueous layer washed with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Flash column chromatography (2.5% MeOH/CH_2Cl_2) afforded the product (**53**) as a yellow solid (2.00 g, 88%). ^1H NMR ($CDCl_3$) : δ

-0.01 (s, 12H, **H1′**, **H2′**), 0.83 (s, 18H, **H3′**, **H5′**, **H6′**), 2.35-2.40 (m, 2H, **H13**), 2.65-2.86 (m, 4H, **H1**), 3.03-3.09 (m, 4H, **H14**), 3.62 (s, 3H, **OMe**), 3.75 (s, 6H, **H16**), 3.95-4.10 (m, 4H, **H11**), 4.24-4.35 (m, 4H, **H12**), 4.58-4.70 (m, 6H, **H8′**, **H11a**), 5.25-5.33 (m, 4H, **H10′**), 5.93-5.97 (m, 2H, **H9′**), 6.33-6.40 (m, 2H, **H3**), 6.74 (s, 2H, **H6**), 7.80 (s, 2H, **H9**), 8.75 (s, 2H, **NH**). ^{13}C NMR ($CDCl_3$): δ -5.52 (**C1′**, **C2′**), 18.0 (**C4′**), 25.7 (**C3′**, **C5′**, **C6′**), 28.7 (**C13**), 33.8 (**C14**), 34.6 (**C1**), 51.9 (**CH_3O**), 56.5 (**C16**), 62.2 (**C11**), 65.2 (**C12**), 65.6 (**C8′**), 105.4 (**C9**), 111.9 (**C6**), 117.9 (**C10′**), 128.2 (**C3**), 132.5 (**C9′**), 143.9 (Q), 150.7 (Q),153.4 (Q), 165.7 (Q), 170.6 (Q). IR (neat): ν = 3402 (OH), 2954, 2857, 1735 (ester), 1726 (Alloc C=O), 1642, 1600, 1526 (C arom), 1469, 1435, 1354, 1256 (CH_3-Si), 1221, 1201 (*t*-Bu), 1112 (*t*-Bu), 1048, 1010, 934, 866, 836, 776 cm^{-1}. MS (FAB) m/z (relative intensity): No parent ion, 496 (10), 482 (9), 455 (11), 441 (13), 232 (12), 206 (19), 204 (10), 200 (14), 192 (34), 188 (23), 172 (33), 165 (18), 152 (17), 150 (16), 149 (100), 147 (17), 140 (20), 131 (18), 103 (22), 91 (47), 89 (27), 87 (36), 80 (33), 75 (42), 73 (77), 61 (39), 57 (53).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[2-amino-*N*-allyloxycarbonyl-5-methoxy-1,4-phenylene)-carbonyl]]-bis[(2*S*)-2-hydroxymethyl-4-methoxycarbonylmethyl-2,3-dihydropyrrole (54)

Hydrofluoric acid.pyridine complex (3.5 mL) was added to a solution of dimer ester (**53**) (740 mg, 0.67 mmol) in THF (10 mL) under a nitrogen atmosphere at 0°C. The reaction was allowed to stir for 30 min at 0°C and then to warm to room temperature over 1 h. The reaction mixture was neutralised with $NaHCO_3$ until

evolution of CO_2 ceased. The product was extracted with DCM (3 x 30 mL), washed with brine (1 x 20 mL) and then dried ($MgSO_4$). Removal of solvent under reduced pressure gave the product as a yellow gum (530 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 2.39 (m, 2H, **H13**), 2.95-2.99 (m, 4H, **H1**), 3.09-3.12 (m, 4H, **H14**), 3.68 (s, 3H, **OMe**), 3.74-3.78 (m, 4H, **H11**), 3.81 (s, 6H, **H16**), 4.28-4.34 (m, 4H, **H12**), 4.62 (d, *J* = 5.5 Hz, 4H, **H8'**), 4.73-4.75 (m, 2H, **H11a)**, 5.31-5.38 (m, 4H, **H10'**), 5.96-6.02 (m, 2H, **H9'**), 6.39-6.50 (m, 2H, **H3**), 6.80 (s, 2H, **H6**), 7.72 (s, 2H, **H9**), 8.57 (s, 2H, **NH**). ^{13}C NMR ($CDCl_3$): δ 28.8 (**C13**), 33.5 (**C14**), 35.5 (**C1**), 52.1 (**CH_3O**), 56.6 (**C16**), 65.3 (**C12**), 66.0 (**C8'**), 105.6 (**C9**), 111.8 (**C6**), 118.1 (**C10'**), 128.1 (**C3**), 132.5 (**C9'**), 144.4 (**Q**), 151.0 (**Q**),153.6 (**Q**), 167.3 (**Q**), 170.7 (**Q**). IR (neat): ν = 3416 (OH), 2953, 1731 (ester), 1726 (Alloc C=O), 1606, 1525 (C arom), 1467, 1434, 1358, 1224, 1048, 938, 870, 768 cm^{-1}. MS (FAB) m/z (relative intensity): 881 ($M^{+\cdot}$, 0.2), 496 (12), 482 (15), 456 (14), 442 (13), 232 (23), 206 (35), 192 (63), 190 (21), 188 (17), 180 (19), 178 (25), 152 (39), 150 (23), 149 (100), 140 (50), 136 (21), 112 (23), 108 (23), 94 (29), 91 (32), 87 (24), 80 (70), 73 (28), 57 (30).

1,1'-[[(Propane-1,3-diyl)dioxy]bis[(*11aS*)-7-methoxy-10-allyloxycarbonyl-(2*S*)-2-methoxycarbonylmethyl-2,3-dihydropyrrole-1,3,11a-trihydro-*5H*-pyrrolo[2,1-c][1,4]bezodiazepin-5-one (55)

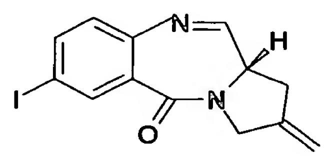
A solution of dimethyl sulphoxide (0.27 mL, 3.82 mmol) in dried DCM (10 mL) was added dropwise over a 15 min period to a stirred, cooled (-45°C) solution of oxalyl chloride (0.17 mL, 1.92 mmol) in DCM (10 mL). After 35 min, a solution of substrate (**54**) (600

mg, 0.68 mmol) in DCM (10 mL) was added dropwise over a period of 15 min to the reaction mixture at −45°C. After 45 min a solution of triethylamine (0.78 mL, 5.42 mmol) in DCM (10 mL) was added over a period of 15 min and the reaction mixture stirred at −45°C for 30 min before being allowed to warm to room temperature over 45 min. The mixture was then diluted with water (10 mL) and the layers separated. The organic layer was washed with 1 M HCl (3 x 50 mL), and brine (1 x 50 mL) before drying ($MgSO_4$) and concentrating *in vacuo*. Flash column chromatography (1.5% $MeOH/CH_2Cl_2$) afforded a yellow glass (457 mg, 78%). $[\alpha]^{20.3}_D$ = +69° (*c* 0.484, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.35–2.63 (m, 2H, **H13**), 2.75–3.10 (m, 4H, **H1**), 3.14–3.19 (m, 4H, **H14**), 3.71 (s, 3H, **OMe**), 3.88 (s, 6H, **H16**), 4.21–4.40 (m, 4H, **H12**), 4.45–4.50 (m, 2H, **H11a**), 4.60–4.62 (m, 4H, **H8′**), 5.26–5.30 (m, 4H, **H10′**), 5.77 (d, *J* = 8.61 Hz, 4H, **H11**) 5.90–5.96 (m, 2H, **H9′**), 6.75–6.80 (m, 2H, **H3**), 6.89 (s, 2H, **H9**), 7.22 (s, 2H, **H6**). ^{13}C NMR ($CDCl_3$): δ 28.8 (**C13**), 33.5 (**C14**), 35.5 (**C1**), 52.1 (**CH_3O**), 56.6 (**C16**), 65.3 (**C12**), 66.0 (**C8′**), 105.6 (**C9**), 111.8 (**C6**), 118.1 (**C10′**), 128.1 (**C3**), 132.5 (**C9′**), 144.4 (**Q**), 151.0 (**Q**),153.6 (**Q**), 167.3 (**Q**), 170.7 (**Q**). IR (neat): ν = 3583, 3412 (OH), 1730 (ester), 1713 (Alloc C=O), 1644, 1421, 1362, 1273, 1223, 1092, 902, 757, 737, 702, 667 cm^{-1}. MS (FAB) m/z (relative intensity): 907 ($M^{+\cdot}$, 1), 456 (6), 245 (7), 232 (16), 218 (13), 206 (23), 205 (10), 204 (14), 192 (42), 190 (17), 178 (22), 177 (10), 176 (16), 166 (17), 165 (10), 164 (16), 152 (23), 151 (12), 150 (18), 149 (100), 140 (16), 93 (18), 91 (22), 89 (13), 87 (26), 80 (58), 75 (19), 73 (28), 57 (25).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[(*11aS*)-7-methoxy-(2*S*)-2-methoxycarbonylmethyl-2,3-dihydropyrrole-1,3,11a-trihydro-*5H*-pyrrolo[2,1-*c*][1,4]bezodiazepin-5-one (56)

A catalytic amount of tetrakistriphenylphosphinepalladium(0) (16 mg, 0.014 mmol) was added to a solution of carbinolamine (**55**) (219 mg, 0.25 mmol), triphenylphosphine (7 mg, 0.025 mmol) and pyrrolidine (0.05 mL, 0.80 mmol) in dry DCM (30 mL) at 0°C. The reaction mixture was stirred for 2 h before being allowed to warm to room temperature over 1 h. The solvent was removed *in vacuo* and the residue was subjected to flash column chromatography (2% MeOH/CH_2Cl_{21} R_f = 0.25) to yield a yellow glass (109 mg, 66%). $[\alpha]^{19.5}{}_D$ = +500° (*c* 0.043, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.17-2.42 (m, 2H, **H13**), 3.15-3.32 (m, 8H, **H1**, **H14**), 3.73 (s, 3H, **OMe**), 3.91 (s, 6H, **H16**), 4.26-4.30 (m, 6H, **H12**, **H11a**), 6.84 (s, 2H, **H9**), 6.92-7.06 (m, 2H, **H3**), 7.47 (s, 2H, **H6**), 7.83 (d, *J* = 4.0 Hz, 4H, **H11**). ^{13}C NMR ($CDCl_3$): δ 28.7 (**C13**), 33.6 (**C14**), 37.4 (**C1**), 52.2 (**CH_3O**), 53.8 (**C11**), 56.2 (**C16**), 65.4 (**C12**), 110.9 (**C9**), 111.8 (**C6**), 126.5 (**C3**), 140.2 (**Q**), 148.0 (**Q**),151.0 (**Q**), 161.4 (**Q**), 162.6 (**C11a**), 170.7 (**Q**). IR (neat): ν = 3583, 3394, 2997, 2950, 1736 (ester), 1717 (Alloc C=O), 1628, 1596, 1511, 1483, 1451, 1431, 1382, 1273, 1245, 1197, 1152, 1068, 995, 963, 914, 842, 753 cm^{-1}. FABMS m/z (relative intensity): 673 ($M^{+\cdot}$, 2), 279 (6), 277 (4), 201 (7), 185 (55), 181 (7), 110 (5), 93 (100), 91 (24), 75 (28), 73 (20), 61 (12), 57 (33).

<u>Example 2(a): Synthesis of the C7-Iodo-C2-methlene PBD Monomer BSD-SJG (64, UP-2023) (see Figure 6)</u>



(*S*)-*N*-(Allyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidenepyrrolidine (57)

Potassium *tert*-butoxide (41.0 mL of a 0.5 M solution in THF, 20.5 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (7.29 g, 20.4 mmol) in THF (20 mL) at 0°C (ice/acetone) under nitrogen. After stirring for 2 h at 0°C, a solution of the ketone **16** (example 1(b)) (3.20 g, 10.2 mmol) in THF (10 mL) was added dropwise and the mixture allowed to warm to room temperature. After stirring for a further 30 min the reaction mixture was diluted with EtOAc (150 mL) and water (150 mL) and the organic layer separated, washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil in which crystals (TPO) formed upon standing in the freezer. Purification by flash chromatography (5% EtOAc/Petroleum Ether) isolated the pure olefin **57** as a colourless oil (2.76 g, 87%): $[\alpha]^{21}_D$ = -22.2 ° (c = 0.25, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 6.02-5.87 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.31 (ddd, 1H, J = 1.65, 3.11, 17.20 Hz, $NCO_2CH_2CH{=}CH_2$), 5.21 (dd, 1H, J = 1.46, 10.40 Hz, $NCO_2CH_2CH{=}CH_2$), 4.99-4.61 (m, 2H, $NCH_2C{=}CH_2$), 4.60 (d, 2H, J = 4.94 Hz, $NCO_2CH_2CH{=}CH_2$), 4.19-3.98 (m, 2H, $NCHCH_2$OTBDMS), 3.93-3.87 (m, 1H, $NCHCH_2$OTBDMS), 3.66-3.42 (m, 2H, $NCH_2C{=}CH_2$), 2.80-2.56 (m, 2H, $NCH_2C{=}CH_2CH_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.03-0.02 (m, 6H,

$Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 154.4 (NC=O), 145.1 and 144.1 ($NCH_2C{=}CH_2$), 133.1 ($NCO_2CH_2CH{=}CH_2$), 117.5 and 117.2 ($NCO_2CH_2CH{=}CH_2$), 107.5 and 106.9 ($NCH_2C{=}CH_2$), 65.8 and 65.6 ($NCO_2CH_2CH{=}CH_2$), 63.7 and 63.1 ($NCHCH_2OTBDMS$), 58.7 and 58.3 ($NCHCH_2OTBDMS$), 51.1 ($NCH_2C{=}CH_2$), 34.9 and 34.2 ($NCH_2C{=}CH_2CH_2$), 25.8 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.5 ($Si(CH_3)_2$); MS (CI), *m/z* (relative intensity) 312 ($M^{+\cdot}$ + 1, 82), 296 (9), 279 (5), 255 (20), 254 ($M{-}OC_3H_5$ or $M{-}^tBu$, 100), 168 (8), 122 (14); IR (Neat) 3083 ($C{=}CH_2$), 2954, 2847, 1709 (NC=O), 1533, 1467, 1404 ($SiCH_3$), 1360, 1310, 1252 ($SiCH_3$), 1207, 1174, 1103, 1076, 1006, 836, 776, 680 cm^{-1}.

(2*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidenepyrrolidine (50)

A catalytic amount of $PdCl_2(PPh_3)_2$ (92 mg, 0.131 mmol) was added to a solution of the allyl carbamate **57** (1.0 g, 3.22 mmol) and H_2O (0.34 mL, 18.9 mmol) in CH_2Cl_2 (30 mL). After 5 min stirring at room temperature, Bu_3SnH (0.96 mL, 1.04 g, 3.57 mmol) was added rapidly in one portion. A slightly exothermic reaction with vigorous gas evolution immediately ensued. The mixture was stirred for 16 h at room temperature under nitrogen at which point TLC (50% EtOAc/Petroleum Ether) revealed the formation of amine. After diluting with CH_2Cl_2 (30 mL), the organic solution was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography (50-100% EtOAc/Petroleum Ether) to afford the amine **58** as a slightly orange oil (0.56 g, 77%): $[\alpha]^{21}_D = -3.9°$ (c = 5.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 4.93 (t, 1H, J = 2.02 Hz, $NCH_2C{=}CH_2$), 4.90 (t,

1H, J = 2.02 Hz, $NCH_2C{=}CH_2$), 3.68-3.46 (m, 4H, $NCHCH_2OTBDMS$ and $NCH_2C{=}CH_2$), 3.30-3.21 (m, 1H, $NCHCH_2OTBDMS$), 2.53-2.41 (m, 2H, $NCH_2C{=}CH_2CH_2$ and NH), 2.26-2.17 (m, 1H, $NCH_2C{=}CH_2CH_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 150.0 ($NCH_2C{=}CH_2$), 104.7 ($NCH_2C{=}CH_2$), 64.7 ($NCHCH_2OTBDMS$), 60.5 ($NCHCH_2OTBDMS$), 51.3 ($NCH_2C{=}CH_2$), 34.9 ($NCH_2C{=}CH_2CH_2$), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), -5.4 ($Si(CH_3)_2$); MS (EI), *m/z* (relative intensity) 227 ($M^{+\cdot}$, 8), 212 (6), 170 ($M-{}^tBu$, 36), 96 (8), 82 ($M-CH_2OTBDMS$, 100), 75 (11); IR (Neat) 3550-3100 (br, NH), 3074 ($C{=}CH_2$), 2929, 2857, 1664 (C=C), 1472, 1424, 1391, 1380, 1361, 1255, 1190, 1101, 1006, 939, 880, 838, 777, 723, 668 cm^{-1}.

(2*S*)-*N*-[5-Iodo-2-(2,2,2-trichloroethyloxycarbonylamino)-benzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidinepyrrolidine (60)

A catalytic amount of DMF (3 drops) was added to a stirred solution of the Troc protected anthranilic acid **59** (0.46 g, 1.04 mmol) and oxalyl chloride (0.10 mL, 0.15 g, 1.15 mmol) in CH_2Cl_2 (30 mL). After 16 h at room temperature the resulting acid chloride solution was added dropwise over 30 min to a stirred mixture of the amine **58** (0.26 g, 1.15 mmol) and TEA (0.26 g, 0.36 mL, 2.58 mmol) in CH_2Cl_2 (15 mL) at -20°C (CCl_4/liq.N_2) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for a further 45 min. At this point TLC analysis (50% EtOAc/Petroleum Ether) revealed complete reaction. The mixture was washed with saturated $NaHCO_3$ (30 mL), saturated NH_4Cl (30 mL), H_2O (25 mL), brine (30 mL), dried

($MgSO_4$), filtered and evaporated *in vacuo* to give the amide **60** as a dark oil (0.65 g, 96%): ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 8.92 (br s, 1H), 8.05-7.88 (m, 1H), 7.74-7.64 (m, 1H), 7.56-7.46 (m, 1H), 5.08-4.95 (m, 2H), 4.84 (d, 1H, J = 11.91 Hz), 4.75 (d, 1H, J = 11.91 Hz), 4.74-4.65 (m, 1H), 4.21-3.68 (m, 4H), 2.96-2.65 (m, 2H), 0.95-0.87 (m, 9H), 0.1-0.03 (m, 6H).

(2*S*)-*N*-(2-Amino-5-iodobenzoyl)-2-(hydroxymethyl)-4-methylidenepyrrolidine (61)

A solution of TBAF (1.24 mL of a 1M solution in THF, 1.24 mmol) was added to the silyl-ether **60** (0.64 g, 0.99 mmol) in THF (15 mL) at 0°C (ice/acetone). The reaction mixture was allowed to warm to room temperature and after 45 min TLC (50% EtOAc/Pet-Ether 40 °- 60 °) revealed the complete disappearance of starting material. Saturated NH_4Cl (75 mL) was added and the reaction mixture extracted with EtOAc (3 X 30 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange oil. Purification by flash chromatography (50% EtOAc/Pet-Ether 40 °- 60 °) provided the pure amino-alcohol 61 as a viscous oil (0.18 g, 51%): ^1H NMR (270 MHz, $CDCl_3$) δ 7.72-7.61 (m, 1H), 7.55-7.40 (m, 1H), 6.51-6.49 (m, 1H), 5.02-4.94 (m, 2H), 4.80-3.80 (m, 8H), 2.81-2.79 (m, 1H), 2.43-2.40 (m, 1H); MS (EI), *m/z* (relative intensity) 359 ($M^{+\cdot}$ + 1, 5), 358 ($M^{+\cdot}$, 33), 328 (3), 327 (10), 254 (3), 247 (11), 246 (100), 218 (18), 164 (2), 127 (4), 120 (4), 119 (10), 113 (9), 112 (91), 94 (2), 91 (20), 90 (5), 82 (10), 67 (2), 64 (3), 63 (3), 52 (3).

(2*S*)-*N*-[5-Iodo-2-(2,2,2-trichloroethyloxycarbonylamino)-benzoyl]-2-(hydroxymethyl)-4-methylidinepyrrolidine (62).

A solution of the amine **61** (179 mg, 0.50 mmol) in CH_2Cl_2 (15 mL) was cooled to 0°C (ice/acetone) and treated with pyridine (81 µL, 79 mg, 1.0 mmol). A solution of 2,2,2-trichloroethylchloroformate (76 µL, 117 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) was then added dropwise to the stirred mixture. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h, at which point TLC (EtOAc) revealed complete consumption of amine **61**. The reaction mixture was washed with saturated $CuSO_4$ (25 mL), H_2O (25 mL), brine (25 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (50% EtOAc/Petroleum Ether) to afford the pure troc-amino compound **62** as an oil (189 mg, 71%): ^1H NMR (270 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 7.75-7.66 (m, 3H), 5.02-4.92 (m, 3H), 4.87 (d, 1H, J = 12.09 Hz), 4.72 (d, 1H, J = 12.09 Hz), 4.15-4.08 (m, 2H), 3.90-3.85 (m, 2H), 3.65-3.63 (m, 1H), 2.80-2.71 (m, 1H), 2.50 (d, 1H, J = 14.83 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.7, 151.9, 142.7, 139.6, 135.6, 134.8, 127.7, 123.4, 108.4, 95.1, 86.6, 74.3, 63.9, 59.0, 53.5, 33.7; MS (EI), *m/z* (relative intensity) 536 (5), 535 (3), 534 (15), 533 ($M^{+\cdot}$, 3), 532 (15), 503 (2), 501 (2), 422 (4), 420 (5), 385 (8), 384 (8), 366 (3), 353 (11), 290 (9), 273 (8), 272 (76), 246 (6), 245 (18), 218 (4), 217 (5), 216 (8), 146 (4), 145 (10), 133 (4), 131 (4), 119 (6), 117 (7), 115 (11), 113 (17), 112 (39), 97 (4), 96 (3), 95 (12), 90 (5), 84 (5), 83 (7), 82 (100), 79 (7), 77 (21), 67 (2), 63 (4), 61 (3), 51 (6); exact mass calcd for $C_{16}H_{16}N_2O_4Cl_3I$ *m/e* 531.9221, obsd *m/e* 531.9155.

(11*S*,11a*S*)-11-Hydroxy-7-iodo-2-methylidene-10-(2,2,2-trichloroethyloxycarbonylamino)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (63)

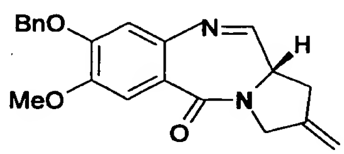
A solution of the alcohol 62 (189 mg, 0.35 mmol) in CH_2Cl_2/CH_3CN (12 mL, 3:1) was treated with 4 Å powdered molecular sieves (100 mg) and NMO (62 mg, 0.53 mmol). After 15 min stirring at room temperature, TPAP (6.2 mg, 17.7 μmol) was added and stirring continued for a further 1 h at which point TLC (50% EtOAc/Petroleum Ether) showed product formation along with some unoxidised starting material. The mixture was then treated with a further quantity of NMO (62 mg, 0.53 mmol) and TPAP (6.2 mg, 17.7 μmol) and allowed to stir for a further 30 min after which time TLC revealed complete reaction. The mixture was evaporated *in vacuo* onto silica and subjected to flash chromatography (40% EtOAc/Petroleum Ether) to provide the protected carbinolamine **63** as a white glass (93 mg, 49%): ^1H NMR (270 MHz, $CDCl_3$) δ 8.09 (d, 1H, J = 2.01 Hz), 7.80 (dd, 1H, J = 8.43, 2.20 Hz), 7.10 (d, 1H, J = 8.43 Hz), 5.60 (d, 1H, J = 9.71 Hz), 5.20-5.04 (m, 3H), 4.79-4.50 (m, 1H), 4.32-4.08 (m, 3H), 3.63 (t, 1H, J = 8.79 Hz), 2.99-2.89 (m, 1H), 2.72 (d, 1H, J = 15.94 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.0, 154.1, 141.0, 140.2, 137.7, 134.5, 133.6, 132.0, 110.4, 94.7, 93.4, 85.7, 75.0, 59.4, 50.7, 35.0; MS (EI), *m/z* (relative intensity) 533 (6), 532 (22), 531 ($M^{+\cdot}$, 8), 530 (17), 529 (10), 449 (5), 383 (6), 354 (7), 353 (5), 338 (6), 325 (5), 290 (5), 274 (15), 273 (8), 272 (43), 254 (5), 245 (8), 218 (5), 216 (12), 147 (5), 146 (6), 145 (9), 133 (10), 131 (9), 128 (5), 127 (15), 119 (11), 117 (5), 97 (6), 95 (9), 92 (6), 91 (6), 90 (6), 83 (11), 82 (100), 81 (7), 80 (8), 75 (5), 63 (7), 53 (5);

exact mass calcd for $C_{16}H_{14}N_2O_4ICl_3$ *m/e* 531.9037, obsd *m/e* 531.8988.

(11a*S*)-7-Iodo-2-methylidene-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (64, UP2023, BSD-SJG).

10% cadmium-lead couple (109 mg, 0.875 mmol) was added to a stirred solution of the Troc-protected carbinolamine 63 (93 mg, 0.175 mmol) in THF (1 mL) and aqueous 1N ammonium acetate (1 mL). After 45 min at room temperature TLC revealed complete reaction (70% EtOAc/Petroleum Ether). The mixture was diluted with EtOAc (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (70% EtOAc/Petroleum Ether) to provide the novel PBD **(64, BSD-SJG, UP2023)** as a white solid (27 mg, 46%): mp °C; ^1H NMR (270 MHz, $CDCl_3$ + CD_3OD) (11*S*,11a*S* isomer) δ 8.10 (d, 1H, *J* = 1.46 Hz), 7.65 (d, 1H, *J* = 8.79 Hz), 6.86 (d, 1H, *J* = 8.06 Hz), 5.14-5.10 (m, 2H), 4.66 (d, 1H, *J* = 5.13 Hz), 4.34 (d, 1H, *J* = 16.12 Hz), 4.23 (d, 1H, *J* = 16.12 Hz), 3.80-3.71 (m, 1H), 3.34 (s, 3H), 3.03-2.86 (m, 1H), 2.65 (d, 1H, *J* = 16.02 Hz); MS (EI), *m/z* (relative intensity) (N10-C11 imine form) 339 ($M^{+\cdot}$ + 1, 20), 338 ($M^{+\cdot}$, 100), 337 (17), 323 (5), 311 (4), 310 (5), 257 (5), 230 (4), 229 (13), 211 (4), 203 (4), 202 (8), 184 (8), 183 (4), 103 (5), 82 (17), 81 (4), 80 (5), 76 (6), 75 (16), 74 (5), 55 (4), 53 (4); IR (NUJOL®) 3295 (br), 2923, 2853, 1716, 1615, 1506, 1457, 1377, 1317, 1278, 1238, 1169, 1118, 1063, 999, 895, 818, 751, 718 cm^{-1}; exact mass calcd for $C_{13}H_{11}N_2OI$ *m/e* 337.9916, obsd *m/e* 337.9870.

Example 2(b): Synthesis of the C8-Benzyl-C7-Methoxy-C2-methlene PBD Monomer SJG-244 (70) (see Figure 7)



(2*S*)-*N*-(4-Benzyloxy-5-methoxy-2-nitrobenzoyl)-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidenepyrrolidine (65)

A catalytic amount of DMF (2 drops) was added to a stirred solution of the nitro-acid **1** (0.645 g, 2.13 mmol) and oxalyl chloride (0.23 mL, 0.33 g, 2.60 mmol) in CH_2Cl_2 (40 mL). After 16 h at room temperature the resulting acid chloride solution was added dropwise to a stirred mixture of the amine **58** (0.522 g, 2.30 mmol) and TEA (0.58 g, 0.80 mL, 5.73 mmol) in CH_2Cl_2 (5 mL) at 0°C (ice/acetone) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for a further 2.5 h. The mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ (50 mL), saturated NH_4Cl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude product as a dark orange oil. Purification by flash chromatography (20% EtOAc/Petroleum Ether) isolated the pure amide **65** as a sticky orange oil (0.86 g, 79%): $[\alpha]^{22}_D$ = -47.2 ° (*c* = 2.79, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.78 and 7.77 (s x 2, $1H_{arom}$), 7.48-7.35 (m, $5H_{arom}$), 6.82 and 6.78 (s x 2, $1H_{arom}$), 5.23 and 5.21 (s x 2, 2H, $PhCH_2O$), 5.09-4.83 (m, 2H, $NCH_2C{=}CH_2$), 4.59-4.49 (m, 1H, $NCHCH_2OTBDMS$), 4.03-3.08 (m, 7H, $NCHCH_2OTBDMS$, $NCH_2C{=}CH_2$ and OCH_3), 2.80-2.56 (m, 2H, $NCH_2C{=}CH_2CH_2$), 0.89 and 0.79 (s x 2, 9H, $SiC(CH_3)_3$), 0.122, -0.11 and -0.14 (s x 3, 6H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz,

$CDCl_3$) (Rotamers) δ 166.2 (N*C*=O), 154.8 and 154.6 (*C*$_{quat}$), 148.2 and 148.0 (*C*$_{quat}$), 144.1 and 143.2 (*C*$_{quat}$), 137.1 (*C*$_{quat}$), 135.3 (*C*$_{quat}$), 128.8 and 128.5 (Bn*C*-H$_{arom}$), 128.2 (*C*$_{quat}$), 127.6 (Bn*C*-H$_{arom}$), 110.1 and 109.2 (*C*-H$_{arom}$), 109.0 and 108.5 (*C*-H$_{arom}$), 107.5 ($NCH_2C{=}CH_2$), 71.3 ($PhCH_2O$), 63.7 ($NCHCH_2OTBDMS$), 60.2 ($NCHCH_2OTBDMS$), 58.1 and 56.6 (OCH_3), 52.8 and 50.5 ($NCH_2C{=}CH_2$), 34.9 and 33.9 ($NCH_2C{=}CH_2CH_2$), 25.8 and 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.4 and -5.6 ($Si(CH_3)_2$); MS (EI), *m/z* (relative intensity) 512 ($M^{+\cdot}$, 3), 497 ($M-CH_3$, 4), 455 (M-^{t}Bu, 100), 380 (2), 364 (5), 286 ($M-NCH_2C{=}CH_2CH_2CHCH_2OTBDMS$, 40), 279 (9), 226 ($NCH_2C{=}CH_2CH_2CHCH_2OTBDMS$, 5), 168 (10), 149 (27), 91 ($PhCH_2$, 62), 73 (8), 57 (9); IR (NEAT) 3066, 3034, 2953, 2856, 2245, 1644 (NC=O), 1578, 1520, 1454, 1426, 1379, 1335, 1276, 1220, 1186, 1106, 1059, 1016, 910, 836, 815, 779, 734, 697, 655, 614 cm^{-1}.

(2*S*)-*N*-(4-Benzyloxy-5-methoxy-2-nitrobenzoyl)-2-(hydroxymethyl)-4-methylidenepyrrolidine (66)

A solution of TBAF (2.10 mL of a 1M solution in THF, 2.10 mmol) was added to the silyl-ether **65** (0.86 g, 1.68 mmol) in THF (20 mL) at 0°C (ice/acetone). The reaction mixture was allowed to warm to room temperature following a colour change (yellow-dark red). After a further 40 min TLC (50% EtOAc/Pet-Ether 40°- 60°) revealed the complete disappearance of starting material. Saturated NH_4Cl (100 mL) was added and the reaction mixture extracted with EtOAc (3 X 40 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark orange oil which was purified by flash chromatography (60% EtOAc/Petroleum Ether) to provide the pure alcohol **66** as a white

solid (0.64 g, 96%): $[\alpha]^{19}_{D}$ = -22.9 ° (*c* = 0.20, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.78 and 7.76 (s x 2, $1H_{arom}$), 7.49-7.33 (m, $5H_{arom}$), 6.91 and 6.82 (s x 2, $1H_{arom}$), 5.22 (s, 2H, $PhCH_2O$), 5.10 (m, 1H, O*H*), 5.03-5.01 (m, 1H, $NCH_2C{=}CH_2$), 4.90-4.85 (m, 1H, $NCH_2C{=}CH_2$), 4.65-4.55 (m, 1H, NC*H*CH_2OH), 3.99 and 3.95 (s x 2, 3H, OCH_3), 3.90-3.72 (m, 4H, $NCHCH_2OH$ and $NCH_2C{=}CH_2$), 2.90-2.87 (m, 1H, $NCH_2C{=}CH_2CH_2$), 2.53-2.47 (m, 1H, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 177.4 (N*C*=O), 155.1 (C_{quat}), 148.3 (C_{quat}), 142.6 (C_{quat}), 137.0 (C_{quat}), 135.2 (C_{quat}), 128.9, 128.6 and 127.6 (Bn*C*-H_{arom}), 109.1 (*C*-H_{arom}), 108.5 (*C*-H_{arom}), 108.3 ($NCH_2C{=}CH_2$), 71.4 ($PhCH_2O$), 65.2 and 63.7 ($NCHCH_2OH$), 60.4 ($NCHCH_2OH$), 56.8 and 56.7 (OCH_3), 53.0 and 50.1 ($NCH_2C{=}CH_2$), 35.1 and 34.4 ($NCH_2C{=}CH_2CH_2$); MS (EI), *m/z* (relative intensity) 398 ($M^{+\cdot}$, 2), 380 (3), 368 (4), 354 (1), 286 (M-$NCH_2C{=}CH_2CH_2CHCH_2OH$, 54), 270 (2), 256 (1), 164 (2), 136 (4), 135 (3), 121 (4), 112 ($NCH_2C{=}CH_2CH_2CHCH_2OH$, 3), 91 ($PhCH_2$, 100), 82 (3), 69 (4), 65 (6); IR (NUJOL®) 3600-3200 (br, OH), 2923, 2853, 1718, 1663, 1611 (NC=O), 1577, 1517, 1460, 1376, 1332, 1275, 1224, 1176, 1052, 990, 925, 886, 862, 796, 759, 723, 702 615 cm^{-1}; exact mass calcd for $C_{21}H_{22}N_2O_6$ *m/e* 398.1478, obsd *m/e* 398.1490.

(2*S*)-*N*-(2-Amino-4-benzyloxy-5-methoxybenzoyl)-2-(hydroxymethyl)-4-methylidenepyrrolidine (67)

The nitro-alcohol **66** (0.637 g, 1.60 mmol), $SnCl_2$ 2H2O (1.81 g, 8.0 mmol) and methanol (36 mL) were heated at reflux and monitored by TLC (90% $CHCl_3$/MeOH). After 1 h the MeOH was evaporated *in vacuo* and the resulting residue cooled (ice), and

treated carefully with saturated $NaHCO_3$ (120 mL). The mixture was diluted with EtOAc (120 mL), and after 16 h stirring at room temperature the inorganic precipitate was removed by filtration through celite. The organic layer was separated, washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an orange glass. Flash chromatography (EtOAc) afforded the pure amine **67** as a pale yellow glass (0.37 g, 63%): $[\alpha]^{23}_D$ = -42.7 ° (c = 3.7, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.44-7.29 (m, $5H_{arom}$), 6.77 (s, $1H_{arom}$), 6.27 (s, $1H_{arom}$), 5.12 (s, 2H, $PhCH_2O$), 5.06-5.00 (m, 1H, $NCH_2C{=}CH_2$), 4.99-4.92 (m, 1H, $NCH_2C{=}CH_2$), 4.63-4.53 (m, 1H, $NCHCH_2OH$), 4.25-3.60 (m, 10H, $NCHCH_2OH$, $NCH_2C{=}CH_2$, OCH_3, OH and NH_2), 2.77 (dd, 1H, J = 8.52, 15.85 Hz, $NCH_2C{=}CH_2CH_2$), 2.43-2.39 (m, 1H, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.4 (NC=O), 151.0 (C_{quat}), 143.3 (C_{quat}), 141.5 (C_{quat}), 140.6 (C_{quat}), 136.5 (C_{quat}), 128.6 and 128.0 (BnC-H_{arom}), 127.8 (C_{quat}), 127.1 (BnC-H_{arom}), 112.5 (C-H_{arom}), 107.8 ($NCH_2C{=}CH_2$), 103.0 (C-H_{arom}), 70.6 ($PhCH_2O$), 65.9 ($NCHCH_2OH$), 60.0 ($NCHCH_2OH$), 57.1 (OCH_3), 53.3 ($NCH_2C{=}CH_2$), 34.4 ($NCH_2C{=}CH_2CH_2$); MS (EI), *m/z* (relative intensity) 368 ($M^{+\cdot}$, 100), 353 ($M-CH_3$, 2), 340 (1), 286 (2), 273 (4), 256 ($M-NCH_2C{=}CH_2CH_2CHCH_2OH$, 59), 249 (8), 226 (4), 200 (2), 196 (2), 166 (5), 138 (17), 112 ($NCH_2C{=}CH_2CH_2CHCH_2OH$, 39), 91 ($PhCH_2$, 70), 82 (5), 65 (5); IR (NEAT) 3600-3000 (br, NH_2 and OH), 3065, 3052, 2932, 2869, 2246, 1668, 1620, 1592, 1513, 1454, 1408, 1264, 1229, 1197, 1176, 1113, 1079, 1002, 909, 733, 698, 645 cm^{-1}; exact mass calcd for $C_{21}H_{24}N_2O_4$ *m/e* 368.1736, obsd *m/e* 368.1662.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4-benzyloxy-5-methoxybenzoyl]-2-(hydroxymethyl)-4-methylidenepyrrolidine (68)

A solution of the amino-alcohol **67** (0.33 g, 0.90 mmol) in CH_2Cl_2 (20 mL) was cooled to 0°C (ice/acetone) and treated with pyridine (0.14 mL, 0.14 g, 1.77 mmol). A solution of allyl chloroformate (87 µL, 99 mg, 0.82 mmol) in CH_2Cl_2 (7 mL) was then added dropwise to the stirred mixture. The reaction mixture was allowed to warm to room temperature and stirred for a further 2.5 h, at which point TLC (EtOAc) revealed complete consumption of amine **67**. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with saturated $CuSO_4$ (40 mL), H_2O (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (80% EtOAc/Petroleum Ether) to afford the pure alloc-amino compound **68** as a white solid (0.34 g, 84%): $[\alpha]^{22}_D = -22.4$ ° (c = 3.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.52 (br s, 1H, N*H*), 7.82 (br s, $1H_{arom}$), 7.49-7.29 (m, $5H_{arom}$), 6.84 (s, $1H_{arom}$), 6.02-5.88 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.39-5.22 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 5.17 (s, 2H, $PhCH_2O$), 5.01 (br s, 1H, $NCH_2C{=}CH_2$), 4.94 (br s, 1H, $NCH_2C{=}CH_2$), 4.64-4.59 (m, 3H, $NCHCH_2OH$ and $NCO_2CH_2CH{=}CH_2$), 4.21-3.60 (m, 8H, $NCHCH_2OH$, $NCH_2C{=}CH_2$, OCH_3 and O*H*), 2.77 (dd, 1H, J = 8.61, 15.94 Hz, $NCH_2C{=}CH_2CH_2$), 2.46 (d, 1H, J = 15.94 Hz, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.4 ($NC{=}O_{amide}$), 153.7 ($NC{=}O_{carbamate}$), 150.3 (C_{quat}), 144.5 (C_{quat}), 143.0 (C_{quat}), 136.2 (C_{quat}), 132.4 ($NCO_2CH_2CH{=}CH_2$), 131.3 (C_{quat}), 128.6, 128.1, and 127.7 (BnC-H_{arom}), 118.1 ($NCO_2CH_2CH{=}CH_2$), 111.1 (C-H_{arom}), 108.1 ($NCH_2C{=}CH_2$), 106.5 (C-H_{arom}), 70.7 ($PhCH_2O$), 65.8 ($NCO_2CH_2CH{=}CH_2$), 65.5 ($NCHCH_2OH$), 59.9 ($NCHCH_2OH$), 56.7 (OCH_3), 54.0 ($NCH_2C{=}CH_2$), 34.1

$(NCH_2C{=}CH_2\mathit{CH}_2)$; MS (EI), *m/z* (relative intensity) 452 ($M^{+\cdot}$, 38), 395 ($M-OC_3H_5$, 4), 394 (10), 340 ($M-NCH_2C{=}CH_2CH_2CHCH_2OH$, 20), 298 (7), 282 (22), 255 (8), 206 (2), 192 (2), 163 (3), 136 (3), 114 (6), 112 ($NCH_2C{=}CH_2CH_2CHCH_2OH$, 12), 91 ($PhCH_2$, 100), 82 (10), 65 (4), 57 (OC_3H_5, 7); IR (NUJOL®) 3600-2000 (br, OH), 3335, 3242, 2922, 2854, 1724, 1614, 1537, 1463, 1407, 1378, 1349, 1280, 1214, 1178, 1117, 1054, 1028, 995, 947, 908, 892, 853, 821, 768, 735, 697, 629, 601, 514 cm^{-1}; exact mass calcd for $C_{25}H_{28}N_2O_6$ *m/e* 452.1947, obsd *m/e* 452.1923.

(11*S*,11a*S*)-10-Allyloxycarbonyl-8-benzyloxy-11-hydroxy-7-methoxy-2-methylidene-1,2,3,10,11,11a-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (69)

A solution of DMSO (0.18 mL, 0.20 g, 2.56 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 30 min to a solution of oxalyl chloride (0.63 mL of a 2.0 M solution in CH_2Cl_2, 1.26 mmol) at -45°C (dry ice/CH_3CN) under a nitrogen atmosphere. After stirring at -45°C for 30 min, a solution of the alcohol **68** (0.42 g, 0.93 mmol) dissolved in CH_2Cl_2 (8 mL) was added dropwise over 35 min at -45°C. After 45 min at -45°C, the mixture was treated dropwise with TEA (0.50 mL, 0.36 g, 3.56 mmol) in CH_2Cl_2 (4 mL) over 30 min at -45°C. After 35 min, the reaction mixture was allowed to warm to room temperature and was diluted with CH_2Cl_2 (30 mL), washed with 1N HCl (20 mL), H_2O (20 mL), brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. TLC (80% EtOAc/Petroleum Ether) of the crude material revealed sufficient product formation and a trace of unoxidised starting material. Purification by flash chromatography (50% EtOAc/Petroleum Ether)

furnished the protected carbinolamine **69** as white glass (0.172 g, 41%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48-7.27 (m, $5H_{arom}$), 7.25 (s, $1H_{arom}$), 6.74 (br s, $1H_{arcm}$), 5.65-5.53 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.56 (d, 1H, J = 9.89 Hz, NCHC*H*OH), 5.22-5.04 (m, 6H, $NCH_2C{=}CH_2$, $NCO_2CH_2CH{=}CH_2$ and $PhCH_2O$), 4.64-4.42 (m, 3H, $NCO_2CH_2CH{=}CH_2$ and O*H*), 4.28 (d, 1H, J = 15.94 Hz, $NCH_2C{=}CH_2$), 4.09 (d, 1H, J = 15.94 Hz, $NCH_2C{=}CH_2$), 3.92 (s, 3H, OCH_3), 3.62 (t, 1H, J = 8.79 Hz, NC*H*CHOH), 2.90 (dd, 1H, J = 8.97, 16.03 Hz, $NCH_2C{=}CH_2CH_2$), 2.67 (d, 1H, J = 16.03 Hz, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.8 ($NC{=}O_{amide}$), 156.0 ($NC{=}O_{carbamate}$), 150.1 (C_{quat}), 149.0 (C_{quat}), 141.8 (C_{quat}), 136.1 (C_{quat}), 131.8 ($NCO_2CH_2CH{=}CH_2$), 128.6, 128.1 and 127.3 ($BnC{-}H_{arom}$), 125.6 (C_{quat}), 118.0 ($NCO_2CH_2CH{=}CH_2$), 114.6 ($C{-}H_{arom}$), 110.6 ($C{-}H_{arom}$), 109.8 ($NCH_2C{=}CH_2$), 85.8 (NCHCHOH), 71.0 ($PhCH_2O$), 66.7 ($NCO_2CH_2CH{=}CH_2$), 59.8 (NCHCHOH), 56.2 (OCH_3), 50.7 ($NCH_2C{=}CH_2$), 35.0 ($NCH_2C{=}CH_2CH_2$); MS (EI), *m/z* (relative intensity) 450 ($M^{+\cdot}$, 24), 422 (1), 392 (1), 364 (1), 348 (3), 340 (12), 298 (6), 282 (8), 257 (2), 229 (2), 192 (3), 178 (2), 164 (4), 136 (3), 110 (3), 91 ($PhCH_2$, 100), 82 (17), 65 (7); IR (NUJOL®) 3600-2500 (br, OH), 2923, 2854, 1711, 1619, 1601, 1513, 1463, 1405, 1377, 1300, 1278, 1202, 1119, 1045, 993, 956, 909, 790, 768, 724, 697, 637 cm^{-1}; exact mass calcd for $C_{25}H_{26}N_2O_6$ *m/e* 450.1791, obsd *m/e* 450.1790.

(11*S*,11a*S*)-10-Allyloxycarbonyl-8-benzyloxy-11-hydroxy-7-methoxy-2-methylidene-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (69)

A solution of the alcohol **68** (0.32 g, 0.71 mmol) in CH_2Cl_2/CH_3CN (30 mL, 3:1) was treated with 4 Å powdered molecular sieves (0.2

g) and NMO (126 mg, 1.08 mmol). After 15 min stirring at room temperature, TPAP (12.6 mg, 35.9 μmol) was added and stirring continued for a further 1 h 20 min at which point TLC (80% EtOAc/Petroleum Ether) revealed product formation along with some unoxidised starting material. The mixture was then treated with a further quantity of NMO (126 mg, 1.08 mmol) and TPAP (12.6 mg, 35.9 μmol), and allowed to stir for a further 0.5 h after which time TLC revealed reaction completion. The mixture was evaporated *in vacuo* onto silica and subjected to flash chromatography (50% EtOAc/Petroleum Ether) to provide the protected carbinolamine 69 as a white glass (153 mg, 48%): $[\alpha]^{23}_{D}$ = +129.8 ° (c = 1.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.48-7.27 (m, $5H_{arom}$), 7.25 (s, $1H_{arom}$), 6.74 (br s, $1H_{arom}$), 5.65-5.53 (m, 1H, $NCO_2CH_2CH{=}CH_2$), 5.56 (d, 1H, J = 9.89 Hz, NCHC*H*OH), 5.22-5.04 (m, 6H, $NCH_2C{=}CH_2$, $NCO_2CH_2CH{=}CH_2$ and $PhCH_2O$), 4.64-4.42 (m, 3H, $NCO_2CH_2CH{=}CH_2$ and O*H*), 4.28 (d, 1H, J = 15.94 Hz, $NCH_2C{=}CH_2$), 4.09 (d, 1H, J = 15.94 Hz, $NCH_2C{=}CH_2$), 3.92 (s, 3H, OCH_3), 3.62 (t, 1H, J = 8.79 Hz, NC*H*CHOH), 2.90 (dd, 1H, J = 8.97, 16.03 Hz, $NCH_2C{=}CH_2CH_2$), 2.67 (d, 1H, J = 16.03 Hz, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.8 ($NC{=}O_{amide}$), 156.0 ($NC{=}O_{carbamate}$), 150.1 (C_{quat}), 149.0 (C_{quat}), 141.8 (C_{quat}), 136.1 (C_{quat}), 131.8 ($NCO_2CH_2CH{=}CH_2$), 128.6, 128.1 and 127.3 ($BnC{-}H_{arom}$), 125.6 (C_{quat}), 118.0 ($NCO_2CH_2CH{=}CH_2$), 114.6 ($C{-}H_{arom}$), 110.6 ($C{-}H_{arom}$), 109.8 ($NCH_2C{=}CH_2$), 85.8 (NCHCHOH), 71.0 ($PhCH_2O$), 66.7 ($NCO_2CH_2CH{=}CH_2$), 59.8 (NCHCHOH), 56.2 (OCH_3), 50.7 ($NCH_2C{=}CH_2$), 35.0 ($NCH_2C{=}CH_2CH_2$); MS (EI), m/z (relative intensity) 450 ($M^{+\cdot}$, 24), 422 (1), 392 (1), 364 (1), 348 (3), 340 (12), 298 (6), 282 (8), 257 (2), 229 (2), 192 (3), 178 (2), 164 (4), 136 (3), 110 (3), 91

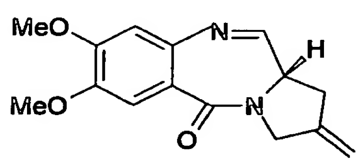
($PhCH_2$, 100), 82 (17), 65 (7); IR (NUJOL®) 3600-2500 (br, OH), 2923, 2854, 1711, 1619, 1601, 1513, 1463, 1405, 1377, 1300, 1278, 1202, 1119, 1045, 993, 956, 909, 790, 768, 724, 697, 637 cm^{-1}; exact mass calcd for $C_{25}H_{26}N_2O_6$ *m/e* 450.1791, obsd *m/e* 450.1790.

(11a*S*)-8-Benzyloxy-7-methoxy-2-methylidene-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (70, SJG-244)

A catalytic amount of tetrakis(triphenylphosphine)palladium (12.0 mg, 10.4 µmol) was added to a stirred solution of the Alloc-protected carbinolamine **69** (0.18 g, 0.40 mmol), triphenylphosphine (5.25 mg, 20 µmol) and pyrrolidine (29 mg, 0.41 mmol) in CH_2Cl_2 (15 mL). After 2 h stirring at room temperature under a nitrogen atmosphere, TLC (98% $CHCl_3$/MeOH) revealed the complete consumption of starting material. The solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography (60% EtOAc/Petroleum Ether) to afford **70** (SJG-244) as a white glass (116 mg, 83%) which was repeatedly evaporated *in vacuo* with $CHCl_3$ in an attempt to provide the N10-C11 imine form: $[\alpha]^{22}_D$ = +754.2 ° (*c* = 0.54, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (mainly imine, plus trace of carbinolamine form) δ 7.70-7.30 (m, 7H, *H*C=N and $6H_{arom}$), 6.84 (s, $1H_{arom}$), 5.25-5.13 (m, 4H, $NCH_2C{=}CH_2$ and $PhCH_2O$), 4.42 (br s, 2H, $NCH_2C{=}CH_2$), 3.95 (s, 3H, OCH_3), 3.88-3.66 (m, 1H, NC*H*HC=N), 3.09 (dd, 1H, *J* = 8.98, 16.12 Hz, $NCH_2C{=}CH_2CH_2$), 2.94-2.87 (m, 1H, $NCH_2C{=}CH_2CH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.7 (N*C*=O), 162.6 (H*C*=N), 150.6 (C_{quat}), 148.1 (C_{quat}), 141.6 (C_{quat}), 140.5 (C_{quat}), 136.1 (C_{quat}), 132.0, 128.7, 128.6, 128.1 and 127.3 (BnC-H_{arom}), 120.1 (C_{quat}), 111.5 (C-H_{arom}), 111.2 (C-H_{arom}), 109.4 ($NCH_2C{=}CH_2$),

70.8 ($PhCH_2O$), 56.2 (OCH_3), 53.7 (NCHHC=N), 51.3 ($NCH_2C=CH_2$), 35.4 ($NCH_2C=CH_2CH_2$); MS (EI), *m/z* (relative intensity) (imine form) 348 ($M^{+\cdot}$, 100), 333 ($M-CH_3$, 42), 319 (3), 269 (5), 257 ($M-PhCH_2$, 25), 241 (11), 229 (56), 227 (11), 213 (5), 186 (4), 156 (6), 136 (22), 122 (4), 91 ($PhCH_2$, 85), 82 (5), 65 (22); IR (NUJOL®) 3318 (br, OH of carbinolamine form), 2923, 2853, 1722, 1668, 1600, 1557, 1504, 1462, 1377, 1261, 1216, 1120, 1003, 892, 789, 722, 695, 623, 542 cm^{-1}; exact mass calcd for $C_{21}H_{20}N_2O_3$ *m/e* 348.1474, obsd *m/e* 348.1469.

Example 2(c) : Synthesis of MMY-SJG (74, UP2064)(see Figure 8)



(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidinepyrrolidine (71)

Potassium *tert*-butoxide (21.2 mL of a 0.5 M solution in THF, 10.6 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (3.78 g, 10.6 mmol) in THF (11 mL) at 0°C (ice/acetone) under nitrogen. After stirring for 2 h at 0°C, a solution of the ketone **38 (Example 1(e))** (2.0 g, 4.07 mmol) in THF (7 mL) was added dropwise and the mixture allowed to warm to room temperature. After stirring for a further 45 min the reaction mixture was diluted with EtOAc (60 mL) and water (60 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark oil. Purification by flash chromatography

(20% EtOAc/Petroleum Ether) isolated the pure olefin **71** as a transparent oil (1.71 g, 86%): $[\alpha]^{22}_{D} = -44.55\,°$ (c = 0.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 8.85 (br s, 1H), 7.86 (s, 1H), 6.82 (s, 1H), 6.03-5.89 (m, 1H), 5.35 (ddd, 1H, J = 17.22, 3.11, 1.47 Hz), 5.24 (ddd, 1H, J = 10.44, 2.75, 1.28 Hz), 4.99-4.92 (m, 2H), 4.70-4.57 (m, 3H), 4.23-3.57 (m, 10H), 2.72-2.68 (m, 2H), 0.96-0.85 (m, 9H), 0.09--0.03 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 168.7, 153.6, 150.9, 143.6, 132.5, 132.2, 118.1, 115.3, 110.6, 107.1, 104.3, 65.7, 63.6, 56.3, 56.0, 33.1, 25.8, 18.1, -5.5 and -5.6; MS (EI), m/z (relative intensity) 492 ($M^{+\cdot}$ + 2, 7), 491 ($M^{+\cdot}$ + 1, 20), 490 ($M^{+\cdot}$, 50), 475 (4), 435 (10), 447 (3), 434 (29), 433 (94), 376 (4), 375 (13), 348 (5), 333 (11), 332 (6), 294 (3), 265 (16), 264 (100), 227 (8), 226 (24), 224 (5), 223 (18), 220 (15), 210 (4), 208 (5), 207 (13), 206 (96), 192 (7), 180 (18), 179 (25), 170 (21), 169 (8), 168 (28), 164 (13), 152 (7), 150 (13), 136 (10), 108 (5), 96 (5), 95 (12), 94 (7), 89 (8), 82 (25), 75 (20), 73 (30), 59 (7), 58 (5), 57 (41), 56 (7), 55 (4); IR (NEAT) 3324 (br, NH), 3082, 2953, 2930, 2857, 1732, 1600, 1523, 1490, 1464, 1419, 1397, 1360, 1333, 1287, 1259, 1228, 1203, 1172, 1115, 1039, 1004, 939, 837, 814, 777 666 cm^{-1}.

(2*S*)-*N*-[(2-Allyloxycarbonylamino)-4,5-dimethoxybenzoyl]-2-(hydroxymethyl)-4-methylidinepyrrolidine (72)

A solution of TBAF (4.29 mL of a 1M solution in THF, 4.29 mmol) was added to the silyl-ether **71** (1.68 g, 3.43 mmol) in THF (45 mL) at 0°C (ice/acetone). The reaction mixture was allowed to warm to room temperature and after 1 h TLC (50% EtOAc/Pet-Ether

40°- 60°) revealed the complete disappearance of starting material. Saturated NH_4Cl (110 mL) was added and the reaction mixture extracted with EtOAc (3 X 50 mL), washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark orange oil. Purification by flash chromatography (99% $CHCl_3$/MeOH) provided the pure alcohol **72** as a white solid (1.15 g, 89%): $[\alpha]^{21}_D = -13.17°$ (c = 0.15, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.69 (s, 1H), 6.82 (s, 1H), 6.03-5.89 (m, 1H), 5.35 (ddd, 1H, J = 17.22, 3.11, 1.65 Hz), 5.24 (ddd, 1H, J = 10.44, 2.75, 1.28 Hz), 5.02-4.94 (m, 2H), 4.66-4.62 (m, 3H), 4.23-3.57 (m, 11H), 2.77 (dd, 1H, J = 15.94, 8.42 Hz), 2.48 (d, 1H, J = 15.94 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.3, 153.8, 151.0, 144.2, 143.1, 132.5, 131.2, 118.1, 115.9, 110.4, 108.1, 104.9, 65.8, 65.1, 59.8, 56.4, 56.0, 54.2, 34.1; MS (EI), *m/z* (relative intensity) 378 ($M^{+\cdot}$ + 2, 3), 377 ($M^{+\cdot}$ + 1, 14), 376 ($M^{+\cdot}$, 51), 319 (3), 265 (10), 264 (62), 263 (4), 259 (8), 224 (4), 223 (18), 220 (17), 208 (5), 207 (14), 206 (100), 192 (8), 190 (5), 180 (27), 179 (29), 178 (4), 164 (23), 163 (4), 152 (12), 151 (6), 150 (19), 137 (5), 136 (22), 135 (6), 125 (6), 120 (6), 113 (6), 112 (31), 109 (6), 108 (11), 95 (4), 94 (9), 82 (28), 80 (8), 67 (5), 57 (5), 54 (7), 53 (7); IR (NUJOL®) 3341 and 3245 (br, OH and NH), 3115, 2918, 2850, 1727, 1616, 1540, 1464, 1399, 1378, 1351, 1283, 1264, 1205, 1179, 1117, 1055, 1040, 996, 946, 909, 894, 855, 823, 768, 754, 722, 696, 623, 602 cm^{-1}; exact mass calcd for $C_{19}H_{24}N_2O_6$ *m/e* 376.1634, obsd *m/e* 376.1614.

(11*S*,11a*S*)-10-Allyloxycarbonyl-7,8-dimethoxy-11-hydroxy-2-methylidene-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (73)

A solution of DMSO (0.75 mL, 0.82 g, 10.5 mmol) in CH_2Cl_2 (27 mL) was added dropwise over 38 min to a solution of oxalyl chloride (2.64 mL of a 2.0 M solution in CH_2Cl_2, 5.27 mmol) at -45°C (liq.N_2/Chlorobenzene) under a nitrogen atmosphere. After stirring at -45°C for 1 h, a solution of the alcohol **72** (1.10 g, 2.93 mmol) in CH_2Cl_2 (27 mL) was added dropwise over 1 h at -45°C. After 1 h at -45°C, the mixture was treated dropwise with a solution of TEA (1.71 mL, 1.24 g, 12.29 mmol) in CH_2Cl_2 (15 mL) over 40 min at -45°C. After a further 30 min, the reaction mixture was allowed to warm to room temperature and was diluted with CH_2Cl_2 (50 mL), washed with 1N HCl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. TLC (80% EtOAc/Petroleum Ether) of the crude material revealed reaction completion. Purification by flash chromatography (60% EtOAc/Petroleum Ether) furnished the protected carbinolamine **73** as a white glass (0.45 g, 41%): $[\alpha]^{22}_D$ = +236.51 ° (*c* = 0.14, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.69 (s, 1H), 5.83-5.81 (m, 1H), 5.60-5.58 (m, 1H), 5.34-5.23 (m, 4H), 4.74-4.66 (m, 1H), 4.50-4.40 (m, 1H), 4.30 (d, 1H, *J* = 15.94 Hz), 4.15 (d, 1H, *J* = 15.93 Hz), 3.96-3.86 (m, 7H), 3.65 (t, 1H, *J* = 8.61 Hz), 2.92 (dd, 1H, 16.21, 9.07 Hz), 2.70 (d, 1H, *J* = 15.94 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.7, 156.0, 150.8, 148.4, 141.8, 131.7, 128.5, 125.2, 118.1, 112.4, 110.3, 109.8, 85.9, 66.8, 59.6, 56.3, 56.1, 50.7, 35.0; MS (EI), *m/z* (relative intensity) 376 ($M^{+\cdot}$ + 2, 6), 375 ($M^{+\cdot}$ + 1, 22), 374 ($M^{+\cdot}$, 100), 346 (5), 293

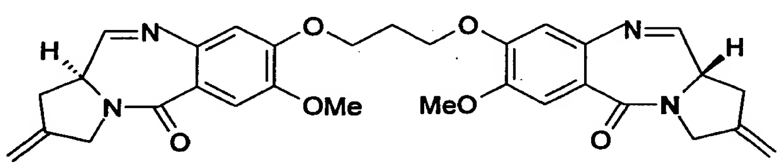
(8), 288 (10), 271 (5), 265 (11), 264 (67), 248 (5), 237 (5), 223 (10), 220 (9), 209 (6), 208 (42), 207 (14), 206 (70), 192 (7), 190 (5), 180 (17), 179 (16), 165 (8), 164 (15), 153 (5), 152 (10), 150 (12), 149 (7), 137 (6), 136 (10), 135 (5), 125 (8), 110 (8), 108 (5), 94 (5), 83 (5), 82 (59), 80 (7), ; IR ($CHCl_3$) 3275 (br, OH), 3075, 2936, 2851, 1706, 1624, 1604, 1516, 1457, 1436, 1403, 1368, 1312, 1301, 1278, 1262, 1218, 1119, 1074, 1045, 940, 916, 893, 867, 851, 666, 637 cm^{-1}; exact mass calcd for $C_{19}H_{22}N_2O_6$ *m/e* 374.1478, obsd *m/e* 374.1687.

(11a*S*)-7,8-Dimethoxy-2-methylidene-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (74, UP2064, MMY-SJG)

A catalytic amount of tetrakis(triphenylphosphine)palladium (32.4 mg, 28.1 µmol) was added to a stirred solution of the Alloc-protected carbinolamine **73** (0.42 g, 1.12 mmol), triphenylphosphine (14.7 mg, 56.2 µmol) and pyrrolidine (83.9 mg, 1.18 mmol) in CH_2Cl_2 (55 mL). After 2.5 h stirring at room temperature under a nitrogen atmosphere, TLC (95% $CHCl_3$/MeOH) revealed the complete consumption of starting material. The solvent was evaporated *in vacuo* and the crude residue was purified by flash chromatography ($CHCl_3$) to afford the novel PBD **(74, MMY-SJG, UP2064)** as a yellow oil which was repeatedly evaporated *in vacuo* with $CHCl_3$ in order to provide the N10-C11 imine form (259 mg, 85%): $[\alpha]^{22}_D = +583.14$ ° (c = 1.42, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 4.39 Hz), 7.51 (s, 1H), 6.82 (s, 1H), 5.21-5.17 (m, 2H), 4.44-4.23 (m, 2H), 3.96-3.81 (m, 7H), 3.17-3.08 (m, 1H), 2.95 (d, 1H, J = 14.29 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 164.7, 162.6, 151.5, 147.6, 141.6, 140.8, 119.8,

111.2, 109.4, 109.4, 56.2, 56.1, 53.8, 51.4, 35.5; MS (EI), *m/z* (relative intensity) 273 ($M^{+\cdot}$ + 1, 16), 272 ($M^{+\cdot}$, 100), 271 (35), 270 (9), 255 (5), 243 (7), 241 (7), 230 (6), 228 (6), 226 (5), 212 (3), 192 (4), 191 (16), 165 (4), 164 (19), 163 (4), 136 (22), 93 (6), 82 (7), 80 (3), 53 (3); IR (NEAT) 3312 (br), 3083, 2936, 2843, 1624, 1603, 1505, 1434, 1380, 1264, 1217, 1180, 1130, 1096, 1069, 1007, 935, 895, 837, 786, 696, 666, 594, 542 cm^{-1}; exact mass calcd for $C_{15}H_{16}N_2O_3$ *m/e* 272.1161, obsd *m/e* 272.1154.

Example 2(d): Synthesis of the PBD Dimer SJG-136 (UP2001) (see Figure 9)



(2*S*)-1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[2-(*tert*-butyldimethylsilyloxymethyl)-4-methylidenepyrrolidine] (75)

A catalytic amount of DMF (2 drops) was added to a solution of the dimer acid 44 (0.66 g, 1.42 mmol) and oxalyl chloride (0.31 mL, 0.45 g, 3.55 mmol) in THF (12 mL). The reaction mixture was stirred for 16 h under nitrogen, concentrated *in vacuo*, and redissolved in THF (10 mL). The resulting solution of *bis*-acid chloride was added dropwise to the amine 58 (0.65 g, 2.86 mmol), H_2O (0.84 mL) and TEA (0.83 mL, 0.60 g, 5.93 mmol) in THF (2 mL) at 0°C (ice/acetone) under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 2 h at which time TLC (EtOAc) revealed reaction

completion. After removal of the THF by evaporation *in vacuo*, the residue was partitioned between H_2O (100 mL) and EtOAc (100 mL). The aqueous layer was washed with EtOAc (3 X 50 mL), and the combined organic layers washed with saturated NH_4Cl (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as a dark orange oil. Purification by flash chromatography (50% EtOAc/Petroleum Ether) afforded the pure amide **75** as a pale yellow glass (0.93 g, 74%): $[\alpha]^{21}_{D}$ = -51.1 ° (*c* = 0.08, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.77 and 7.74 (s x 2, $2H_{arom}$), 6.81 and 6.76 (s x 2, $2H_{arom}$), 5.09-4.83 (m, 4H, $NCH_2C{=}CH_2$), 4.60 (m, 2H, $NCHCH_2OTBDMS$), 4.35-4.31 (m, 4H, $OCH_2CH_2CH_2O$), 4.08-3.74 (m, 14H, $NCHCH_2OTBDMS$, $NCH_2C{=}CH_2$ and OCH_3), 2.72-2.45 (m, 6H, $NCH_2C{=}CH_2CH_2$ and $OCH_2CH_2CH_2O$), 0.91 and 0.79 (s x 2, 18H, $SiC(CH_3)_3$), 0.09, -0.09, and -0.12 (s x 3, 12H, $Si(CH_3)_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 166.2 (NC=O), 154.7 and 154.5 (C_{quat}), 148.4 and 148.2 (C_{quat}), 144.1 and 143.2 (C_{quat}), 137.2 (C_{quat}), 128.2 and 127.4 (C_{quat}), 110.1 and 108.6 ($C\text{-}H_{arom}$), 109.1 and 108.3 ($C\text{-}H_{arom}$), 107.5 ($NCH_2C{=}CH_2$), 65.7 and 65.5 ($OCH_2CH_2CH_2O$), 63.9 and 62.6 ($NCHCH_2OTBDMS$), 60.2 ($NCHCH_2OTBDMS$), 58.1 and 56.6 (OCH_3), 52.8 and 50.5 ($NCH_2C{=}CH_2$), 35.0 and 33.9 ($NCH_2C{=}CH_2CH_2$), 30.8 and 28.6 ($OCH_2CH_2CH_2O$), 25.8 and 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), -5.5 and -5.6 ($Si(CH_3)_2$); MS (EI), *m/z* (relative intensity) 885 ($M^{+\cdot}$, 7), 828 ($M\text{-}^tBu$, 100), 740 ($M\text{-}CH_2OTBDMS$, 20), 603 (3), 479 (26), 391 (27), 385 (25), 301 (7), 365 (10), 310 (14), 226 (8), 222 (13), 170 (21), 168 (61), 82 (39), 75 (92); IR (NUJOL®) 2923, 2853, 2360, 1647, 1587, 1523 (NO_2), 1461, 1429, 1371, 1336 (NO_2), 1277, 1217, 1114, 1061, 1021, 891, 836 772, 739 cm^{-1}.

(2*S*)-1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethyl)-4-methylidenepyrrolidine] (76)

A solution of TBAF (3.98 mL of a 1M solution in THF, 3.98 mmol) was added to the *bis*-silyl ether **75** (1.41 g, 1.59 mmol) in THF (35 mL) at 0°C (ice/acetone). The reaction mixture was allowed to warm to room temperature and after a further 30 min saturated NH_4Cl (120 mL) was added. The aqueous solution was extracted with EtOAc (3 X 80 mL), washed with brine (80 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark orange oil which was purified by flash chromatography (97% $CHCl_3$/MeOH) to provide the pure diol **76** as a light orange solid (0.98 g, 94%): $[\alpha]^{19}_D$ = -31.9 ° (c = 0.09, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) (Rotamers) δ 7.75 and 7.71 (s x 2, $2H_{arom}$), 6.96 and 6.84 (s x 2, $2H_{arom}$), 5.08, 5.02 and 4.88 (br s x 3, 4H, $NCH_2C{=}CH_2$), 4.61-4.50 (m, 2H, $NCHCH_2OH$), 4.35-4.33 (m, 4H, $OCH_2CH_2CH_2O$), 4.02-3.65 (m, 14H, $NCHCH_2OH$, $NCH_2C{=}CH_2$ and OCH_3), 2.88-2.43 (m, 6H, $NCH_2C{=}CH_2CH_2$ and $OCH_2CH_2CH_2O$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (Rotamers) δ 167.9 and 166.9 (NC=O), 154.9 and 154.3 (C_{quat}), 148.4 and 148.2 (C_{quat}), 143.3 and 142.6 (C_{quat}), 137.2 and 137.0 (C_{quat}), 127.6 and 127.3 (C_{quat}), 109.1 (C-H_{arom}), 108.4 ($NCH_2C{=}CH_2$), 108.2 (C-H_{arom}), 65.6 and 65.4 ($OCH_2CH_2CH_2O$), 64.5 and 63.3 ($NCHCH_2OH$), 60.5 and 60.0 ($NCHCH_2OH$), 56.8 and 56.7 (OCH_3), 52.9 ($NCH_2C{=}CH_2$), 35.0 and 34.3 ($NCH_2C{=}CH_2CH_2$), 29.6 and 28.6 ($OCH_2CH_2CH_2O$); MS (FAB) (Relative Intensity) 657 ($M^{+\cdot}$ + 1, 10), 639 (M-OH, 2), 612 (1), 544 (M-$NCH_2CCH_2CH_2CHCH_2OH$, 4), 539 (1), 449 (16), 433(9), 404 (8), 236 (32), 166 (65), 151 (81), 112 (82), 82 (100); IR (NUJOL®) 3600-3200 (br, OH), 2923, 2853, 2360, 1618, 1582, 1522 (NO_2), 1459,

1408, 1375, 1335 (NO_2), 1278, 1218, 1061, 908, 810, 757 cm^{-1}.

(2*S*)-1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethyl)-4-methylidenepyrrolidine] (77)

A mixture of the diol **76** (0.98 g, 1.49 mmol) and $SnCl_2.2H_2O$ (3.36 g, 14.9 mmol) in MeOH (35 mL) was heated at reflux and the progress of the reaction monitored by TLC (90% $CHCl_3$/MeOH). After 45 min, the MeOH was evaporated *in vacuo* and the resulting residue was cooled (ice), and treated carefully with saturated $NaHCO_3$ (120 mL). The mixture was diluted with EtOAc (120 mL), and after 16 h stirring at room temperature the inorganic precipitate was removed by filtration through celite. The organic layer was separated, washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown solid. Flash chromatography (95% $CHCl_3$/MeOH) afforded the pure *bis*-amine **77** as an orange solid (0.54 g, 61%): $[\alpha]^{19}_D = -31.8\,°$ (c = 0.30, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.74 (s, $2H_{arom}$), 6.32 (s, $2H_{arom}$), 5.00 (br s, 2H, $NCH_2C{=}CH_2$), 4.93 (br s, 2H, $NCH_2C{=}CH_2$), 4.54 (br s, 2H, $NCHCH_2OH$), 4.24-4.14 (m, 4H, $OCH_2CH_2CH_2O$), 3.98-3.50 (m, 14H, $NCHCH_2OH$, $NCH_2C{=}CH_2$ and OCH_3), 2.76 (dd, 2H, J = 8.61, 15.91 Hz, $NCH_2C{=}CH_2CH_2$), 2.46-2.41 (m, 2H, $NCH_2C{=}CH_2CH_2$), 2.33-2.28 (m, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.0 (NC=O), 151.0 (C_{quat}), 143.5 (C_{quat}), 141.3 (C_{quat}), 140.6 (C_{quat}), 112.4 (C-H_{arom}), 111.9 (C_{quat}), 107.8 ($NCH_2C{=}CH_2$), 102.4 (C-H_{arom}), 65.2 ($OCH_2CH_2CH_2O$), 65.0 ($NCHCH_2OH$), 59.8 ($NCHCH_2OH$), 57.1 (OCH_3), 53.3 ($NCH_2C{=}CH_2$), 34.4 ($NCH_2C{=}CH_2CH_2$), 29.0 ($OCH_2CH_2CH_2O$); MS (FAB) (Relative Intensity) 596 ($M^{+\cdot}$, 13), 484 (M-

$NCH_2CCH_2CH_2CHCH_2OH$, 14), 389 (10), 371 (29), 345 (5), 224 (8), 206 (44), 166 (100), 149 (24), 112 (39), 96 (34), 81 (28); IR (NUJOL®) 3600-3000 (br, OH), 3349 (NH_2), 2922, 2852, 2363, 1615, 1591 (NH_2), 1514, 1464, 1401, 1359, 1263, 1216, 1187, 1169, 1114, 1043, 891, 832, 761 cm^{-1}.

(2*S*,4*R*)&(2*S*,4*S*)-1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethyl)-4-methylpyrrolidine] (77a).

A solution of hydrazine (23 mg, 23 µL, 0.72 mmol) in MeOH (5 mL) was added dropwise to a solution of the diol **76** (95 mg, 0.145 mmol) and Raney Ni (20 mg) in MeOH (15 mL) heated at reflux. After 1 h at reflux TLC (90% $CHCl_3$/MeOH) revealed some amine formation. The reaction mixture was treated with further Raney Ni (20 mg) and hydrazine (23 mg, 23 µL, 0.72 mmol) in MeOH (5 mL) and was heated at reflux for an additional 30 min at which point TLC revealed complete reaction. The reaction mixture was then treated with enough Raney Ni to decompose any remaining hydrazine and heated at reflux for a further 1.5 h. Following cooling to room temperature the mixture was filtered through a sinter and the resulting filtrate evaporated *in vacuo*. The resulting residue was then treated with CH_2Cl_2 (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide the bis-amine 77**a** as a yellow oil (54 mg, 63%): ^1H NMR (270 MHz, $CDCl_3$) (diastereoisomers) δ 6.73 (s, $2H_{arom}$), 6.32 (s, $2H_{arom}$), 4.60-4.30 (m, 2H, $NCHCH_2OH$), 4.19 (t, 4H, J = 5.87 Hz, $OCH_2CH_2CH_2O$), 3.78-3.50 (m, 14H, $NCHCH_2OH$, NCH_2CHCH_3 and OCH_3), 2.40-1.55 (m, 8H, NCH_2CHCH_3, $OCH_2CH_2CH_2O$ and $NCH_2CHCH_3CH_2$), 1.00-0.95 (m, 6H,

NCH_2CHCH_3); MS (EI), *m/z* (relative intensity) 600 ($M^{+\cdot}$, 16), 459 (46), 345 (16), 206 (13), 186 (17), 180 (31), 166 (37), 149 (6), 142 (76), 100 (6), 98 (13), 97 (29), 84 (81), 69 (7), 55 (100).

(2*S*)-1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-allyloxycarbonylamino-5-methoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethyl)-4-methylidenepyrrolidine] (78)

Pyridine (0.47 mL, 0.46 g, 5.82 mmol) was added to a stirred solution of the *bis*-amine **77** (0.857 g, 1.44 mmol) in CH_2Cl_2 (30 mL) at 0°C (ice/acetone). The cool mixture was then treated dropwise with a solution of allyl chloroformate (0.33 mL, 0.38 g, 3.15 mmol) in CH_2Cl_2 (10 mL). After 2.5 h stirring at room temperature, the mixture was diluted with CH_2Cl_2 (60 mL), washed with 1N HCl (2 X 50 mL), H_2O (80 mL), brine (80 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (70-100% EtOAc/Petroleum Ether) to afford the allyl cartamate compound **78** as a slightly orange glass (0.548 g, 50%): ^1H NMR (270 MHz, $CDCl_3$) δ 8.58 (br s, 2H, N*H*), 7.56 (s, $2H_{arom}$), 6.78 (s, $2H_{arom}$), 6.03-5.88 (m, 2H, $NCO_2CH_2CH{=}CH_2$), 5.39-5.21 (m, 4H, $NCO_2CH_2CH{=}CH_2$), 5.00 (br s, 2H, $NCH_2C{=}CH_2$), 4.93 (br s, 2H, $NCH_2C{=}CH_2$), 4.70-4.57 (m, 4H, $NCO_2CH_2CH{=}CH_2$), 4.30-4.25 (m, 4H, $OCH_2CH_2CH_2O$), 4.17-3.90 (m, 8H, $NCHCH_2OH$ and $NCH_2C{=}CH_2$), 3.81-3.54 (m, 8H, $NCHCH_2OH$ and OCH_3), 2.76 (dd, 2H, *J* = 8.52, 15.85 Hz, $NCH_2C{=}CH_2CH_2$), 2.49-2.44 (m, 2H, $NCH_2C{=}CH_2CH_2$), 2.36-2.28 (m, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.3 ($NC{=}O_{amide}$), 153.8 ($NC{=}O_{carbamate}$), 150.5 (C_{quat}), 144.8 (C_{quat}), 143.1 (C_{quat}), 132.5 ($NCO_2CH_2CH{=}CH_2$), 130.7 (C_{quat}), 118.1 ($NCO_2CH_2CH{=}CH_2$), 116.8 (C_{quat}), 110.9 ($C\text{-}H_{arom}$),

108.1 ($NCH_2C=CH_2$), 106.9 (C-H_{arom}), 65.7 ($NCO_2CH_2CH=CH_2$), 65.4 ($OCH_2CH_2CH_2O$), 65.1 ($NCHCH_2OH$), 59.8 ($NCHCH_2OH$), 56.5 (OCH_3), 53.9 ($NCH_2C=CH_2$), 34.2 ($NCH_2C=CH_2CH_2$), 29.7 and 29.2 ($OCH_2CH_2CH_2O$); MS (FAB) (Relative Intensity) 765 ($M^{+\cdot}$ + 1, 10), 652 (M-$NCH_2CCH_2CH_2CHCH_2OH$, 32), 594 (4), 539 (2), 481 (51), 441 (31), 290 (3), 249 (13), 232 (38), 192 (83), 166 (49), 149 (32), 114 (100).

1,1′-[[(Propane-1,3-diyl)dioxy]bis[(11*S*,11a*S*)-10-(allyloxycarbonyl)-11-hydroxy-7-methoxy-2-methylidene-1,2,3,10,11,11a-hexahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one] (79)

A solution of the *bis*-alloc compound **78** (150 mg, 0.196 mmol) in CH_2Cl_2/CH_3CN (12 mL, 3:1) was treated with 4 Å powdered molecular sieves (0.2 g) and NMO (70 mg, 0.598 mmol). After 15 min stirring at room temperature, TPAP (7 mg, 19.9 µmol) was added and stirring continued for a further 2 h at which time TLC (95% $CHCl_3$/MeOH) indicated formation, of the fully cyclised product along with the presumed semi-cyclised product **79a**, and unreacted starting material **78** present in the reaction mixture. The mixture was then treated with a further quantity of NMO (35 mg, 0.299 mmol) and TPAP (3.5 mg, 9.96 µmol), and allowed to stir for a further 0.5 h when TLC revealed reaction completion. The solvent was evaporated *in vacuo* and the black residue was subjected to flash chromatography (98% $CHCl_3$/MeOH) to provide the pure protected carbinolamine **79** as a white solid (47 mg, 32%): ^1H NMR (270 MHz, $CDCl_3$) δ 7.23 (s, $2H_{arom}$), 6.74 (s, $2H_{arom}$), 5.90-5.65 (m, 2H, $NCO_2CH_2CH=CH_2$), 5.57 (d, 2H, J = 8.24 Hz, NCHC*H*OH),

5.26-5.07 (m, 8H, $NCH_2C=CH_2$ and $NCO_2CH_2CH=CH_2$), 4.67-4.10 (m, 14H, $NCO_2CH_2CH=CH_2$, $NCH_2C=CH_2$, $OCH_2CH_2CH_2O$ and OH), 3.89 (s, 6H, OCH_3), 3.63 (m, 2H, NCHCHOH), 2.91 (dd, 2H, J = 8.79, 15.76 Hz, $NCH_2C=CH_2CH_2$), 2.68 (d, 2H, J = 16.10 Hz, $NCH_2C=CH_2CH_2$), 2.42-2.24 (m, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.7 ($NC=O_{amide}$), 150.1 (C_{quat}), 149.0 (C_{quat}), 141.7 (C_{quat}), 131.7 ($NCO_2CH_2CH=CH_2$), 130.6 (C_{quat}), 128.9 (C_{quat}), 128.8 (C_{quat}), 118.3 ($NCO_2CH_2CH=CH_2$), 114.7 ($C-H_{arom}$), 110.7 ($C-H_{arom}$), 109.8 ($NCH_2C=CH_2$), 85.9 (NCHCHOH), 66.9 ($NCO_2CH_2CH=CH_2$), 66.0 ($OCH_2CH_2CH_2O$), 59.7 (NCHCHOH), 56.1 (OCH_3), 50.7 ($NCH_2C=CH_2$), 35.0 ($NCH_2C=CH_2CH_2$), 29.7 and 29.1 ($OCH_2CH_2CH_2O$); MS (FAB) (Relative Intensity) 743 ($M^{+\cdot}$ - 17, 16), 725 (17), 632 (13), 574 (8), 548 (13), 490 (10), 481 (9), 441 (7), 425 (6), 257 (12), 232 (20), 192 (46), 166 (52), 149 (100), 91 (59); IR (NUJOL®) 3234 (br, OH), 2923, 2853, 2361, 1707, 1604, 1515, 1464, 1410, 1377, 1302, 1267, 1205, 1163, 1120, 1045, 999, 955, 768, 722 cm^{-1}.

1,1′-[[(Propane-1,3-diyl)dioxy]bis[(11a*S*)-7-methoxy-2-methylidene-1,2,3,11a-tetrahydro-*5H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one] (80, SJG-136)

A catalytic amount of tetrakis(triphenylphosphine)palladium (11 mg, 9.52 μmol) was added to a stirred solution of the *bis*-alloc-carbinolamine **79** (139 mg, 0.183 mmol), triphenylphosphine (4.8 mg, 18.3 μmol) and pyrrolidine (27 mg, 0.380 mmol) in CH_2Cl_2/CH_3CN (13 mL, 10:3) at 0°C (ice/acetone) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and the progress monitored by TLC (95% $CHCl_3$/MeOH). After 2 h 15 min TLC revealed the reaction was complete,

proceeding *via* the presumed half-imine product **261**, to give a TLC spot which fluoresced brightly under UV. The solvent was evaporated *in vacuo* and the resulting residue subjected to flash chromatography (98% $CHCl_3$/MeOH) to give the *bis*-imine target molecule **80** (SJG-136) as a pale orange glass (78 mg, 77%) which was repeatedly evaporated *in vacuo* with $CHCl_3$ to provide the imine form: $[\alpha]^{21}{}_D$ = +357.7 ° (*c* = 0.07, $CHCl_3$); Reverse Phase HPLC (C_4 stationary phase, 65% MeOH/H_2O mobile phase, 254 nm), Retention time = 6.27 min, % Peak area = 97.5%; ^1H NMR (270 MHz, $CDCl_3$) (imine form) δ 7.68 (d, 2H, *J* = 4.4 Hz, *H*C=N), 7.49 (s, $2H_{arom}$), 6.85 (s, $2H_{arom}$), 5.20 (s, 2H, $NCH_2C{=}CH_2$), 5.17 (s, 2H, $NCH_2C{=}CH_2$), 4.46-4.19 (m, 4H, $OCH_2CH_2CH_2O$), 3.92 (s, 6H, OCH_3), 3.89-3.68 (m, 6H, $NCH_2C{=}CH_2$ and NC*H*HC=N), 3.12 (dd, 2H, *J* = 8.61, 16.21 Hz, $NCH_2C{=}CH_2CH_2$), 2.68 (d, 2H, *J* = 16.30 Hz, $NCH_2C{=}CH_2CH_2$), 2.45-2.38 (m, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR (67.8 MHz, $CDCl_3$) (imine form) δ 164.7 (NC=O), 162.6 (HC=N), 150.7 (C_{quat}), 147.9 (C_{quat}), 141.5 (C_{quat}), 140.6 (C_{quat}), 119.8 (C_{quat}), 111.5 ($C{-}H_{arom}$), 110.7 ($C{-}H_{arom}$), 109.4 ($NCH_2C{=}CH_2$), 65.4 ($OCH_2CH_2CH_2O$), 56.1 (OCH_3), 53.8 (NCHHC=N), 51.4 ($NCH_2C{=}CH_2$), 35.4 ($NCH_2C{=}CH_2CH_2$), 28.8 ($OCH_2CH_2CH_2O$); MS (FAB) (Relative Intensity) (imine form) 773 ($M^{+\cdot}$ + 1 + (Thioglycerol adduct X 2), 3), 665 ($M^{+\cdot}$ + 1 + Thioglycerol adduct, 7), 557 ($M^{+\cdot}$ + 1, 9), 464 (3), 279 (12), 257 (5), 201 (5), 185 (43), 166 (6), 149 (12), 93 (100); IR (NUJOL®) 3600-3100 (br, OH of carbinolamine form), 2923, 2849, 1599, 1511, 1458, 1435, 1391, 1277, 1228, 1054, 1011, 870, 804, 761, 739 cm^{-1}.

Example 2(e): Synthesis of PBD with ketone on C-ring (172, UP-2067) (see Figure 10)

(2S)(4R)-N-[4-benzyloxy-5-methoxy-2-(2', 2', 2'-trichloroethoxy)carbonyl]-2-(tert-butyldimethylsilyloxymethyl)-4-hydroxypyrrolidine (168)

A solution of 2,2,2-trichloroethylchloroformate (8.74 g, 5.68 mL, 41.2 mmol) in dichloromethane (50 mL) was added to a solution of **4** (18.2g, 37.5 mmol) and pyridine (5.92 g, 6.1 mL, 75.0 mmol) in dry dichloromethane (200 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at room temperature and was then washed with saturated copper sulphate solution (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over magnesium sulphate, filtered and excess solvent removed by rotary evaporation to afford the product **168** (22.01 g, 33.2 mmol, 89%) which was used in the subsequent reaction without further purification. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.31 (bs, 1H); 7.48 (s, 1H); 7.45-7.28 (m, 5H); 6.82 (s, 1H); 5.17 (bs, 2H); 4.89 (d, J = 11.9 Hz, 1H); 4.70 (d, J = 11.9 Hz, 1H); 4.56 (bs, 1H); 4.40 (bs, 1H); 4.20-4.00 (m, 1H); 3.95-3.40 (m, 7H); 2.40-2.00 (m, 2H); 0.09 (s,9H); 0.04 (s, 6H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.2, 152.1, 150.2, 136.1, 128.6, 128.1, 127.7, 111.6, 106.2, 95.2, 74.4, 70.7, 70.5, 62.1, 57.2, 56.4, 35.4, 25.8, 18.1, -5.46.

(2S)-N-[4-benzyloxy-5-methoxy-2-(2', 2', 2'-trichloroethoxy)carbonyl amino]-2-(tert-butyldimethylsilyloxymethyl)-4-oxopyrrolidine (169)

A solution of DMSO (7.80 g, 99.8 mmol) in dry dichloromethane

(18 mL) was added dropwise, over 30 minutes, to a solution of oxalyl chloride (6.34 g, 49.9 mmol) in dry dichloromethane (25 mL) at − 45°C under a nitrogen atmosphere and the reaction mixture allowed to stir for a further 15 minutes. A solution of the substrate **168** (22.01 g, 33.3 mmol) in dichloromethane (50 mL) was added dropwise over 40 minutes to the reaction mixture, which was then allowed to stir for 45 minutes at − 45°C. Finally, neat triethylamine (23.52 g, 232.9 mmol) was added dropwise over 30 minutes and the reaction mixture allowed to stir at -45°C for 15 minutes. The reaction mixture was allowed to warm to room temperature, diluted with water (150 mL) and the organic phase washed with dilute HCl (1N, 100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo* to afford the crude product which was subjected to column chromatography (ethyl acetate/40-60 petroleum ether, 50:50). Removal of excess eluent afforded the product (20.15 g, 92% yield). ^{1}H NMR (270 MHz, CDCl3) δ 7.88 (bs, 1H); 7.49-7.28 (m, 5H); 6.80 (s, 1H); 5.22 (d, J = 12.1 Hz, 1H); 5.17 (d, J = 12.1 Hz, 1H); 4.80 (bs, 2H); 4.10-3.60 (m, 8H); 2.75 (dd, J = 18.0, 9.5 Hz, 1H); 2.52 (d, J = 18.0 Hz, 1H); 0.87 (s, 9H); 0.06 (s, 3H); 0.05 (s, 3H). ^{13}C NMR (67.8 MHz) δ 208.7, 168.8, 151.8, 150.6, 144.7, 136.0, 128.5, 128.1, 127.7, 110.9, 106.4, 95.2, 74.4, 70.7, 66.0, 56.8, 56.4, 39.4, 25.8, 18.0, -5.7.

(2S)-N-[4-benzyloxy-5-methoxy-2-(2', 2', 2'-trichloroethoxy)carbonyl amino]-2-(hydroxymethyl)-4-oxopyrrolidine (170)

Glacial acetic acid (60 mL) and water (20 mL) were added to a solution of ketone **169** (9.44 g, 14.3 mmol) in THF (20 mL) and the reaction mixture allowed to stir for 3 hr. (reaction complete by TLC). The reaction mixture was diluted with dichloromethane (200 mL) and neutralized dropwise with sat. sodium bicarbonate (1.5 L) in a 5 L flask (effervescence!). The phases were allowed to separate and the aqueous layer extracted with dichloromethane (2 x 100 mL). The combined organic layers were washed with brine and dried over magnesium sulphate. Removal of excess solvent afforded the crude product which was subjected to column chromatography on silica (ethyl acetate/40-60 petroleum ether, 50:50) to give the pure product (6.44 g, 83%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.77 (bs, 1H); 7.57 (s, 1H); 7.46-7.28 (m, 5H); 6.83 (s,1H); 5.13 (s, 2H); 4.85-4.70 (m, 3H); 4.07-3.60 (m, 7H); 2.77 (dd, J = 18.5, 9.5 Hz, 1H); 2.54 (d, J = 18.5Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 209.0, 169.4, 152.3, 150.6, 145.5, 136.0, 130.0, 128.6, 128.3, 127.6, 110.9, 107.4, 95.2, 74.5, 70.8, 64.4, 60.4, 56.6, 55.9, 39.5.

(11s, 11aS)-4-benzyloxy-11-hydroxy-5-methoxy-4-oxo-10-(2', 2', 2'-trichloroethoxy)carbonyl-amino 1, 10, 11, 11a-tetrahydro-5H-pyrrolo-[2,1-c][1,4]benzodiazepin-5-one (171)

A solution of DMSO (4.45 g, 4.04 mL, 56.9 mmol) in dry dichloromethane (25 mL) was added dropwise, over 5 minutes, to a solution of oxalyl chloride (3.58 g, 49.9 mmol) in dry

dichloromethane (14 mL) at -60°C under a nitrogen atmosphere and the reaction mixture allowed to stir for a further 15 minutes. A solution of the substrate **170** (10.93 g, 20.0 mmol) in dichloromethane (25 mL) was added dropwise over 30 minutes to the reaction mixture, which was then allowed to stir for 30 minutes at -60°C. Finally, neat triethylamine (11.15 g, 232.9 mmol) was added dropwise over 30 minutes and the reaction mixture allowed to stir at -60°C for 15 minutes. The reaction mixture was allowed to warm to room temperature, diluted with water (150 mL) and the organic phase washed with dilute HCl (1N, 100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over magnesium sulphate, filtered and concentrated in vacuo to afford the crude product which was subjected to column chromatography (ethyl acetate/40-60 petroleum ether, 50:50). Removal of excess eluent afforded the product **171** (9.66 g, 89 % yield). ^1H NMR (270 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H); 7.27 (s, 1H); 6.95 (s, 1H); 5.76 (d, J = 9.9 Hz, 1H); 5.52- 5.00 (m, 3H), 4.33 (d, J = 6.8 Hz, 1H); 4.30 (d, J = 19.2 Hz, 1H); 4.00-3.70 (m, 5H); 2.98 (dd, J = 20.0, 10.4 Hz, 1H); 2.94 (d, J = 20.0 Hz, 1H). ^{13}C NMR (67.8 MHz) δ 207.7, 167.5, 154.5, 152.6, 150.8, 149.6, 135.8, 128.9-127.3, 124.0, 114.5, 110.8, 95.0, 86.6, 75.0, 71.1, 56.8, 56.2, 52.6, 40.2.

(11aS)-4-benzyloxy-5-methoxy-4-oxo-1,10,11,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (172)

Cadmium/lead couple (1.15 g) was added to a solution of cyclized ketone (1 g, 1.84 mmol) in THF (5 mL) and aqueous ammonium acetate (1N, 15 mL). The reaction mixture was allowed to stir

for 90 minutes and then filtered through celite. The celite pad was washed with ethyl acetate (2 x 25 mL) and the organic layer separated. The organic layer was washed with brine (50 mL) and dried over magnesium sulphate. Removal of excess solvent followed by column chromatography afforded the pyrrolobenzodiazepine **172** (0.324 g, 0.93 mmol). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.75 (d, J = 4.4 Hz, 1H); 7.51 (s, 1H); 7.46-7.27 (m, 5H); 5.23 (d, J = 12.3 Hz, 1H); 5.17 (d, J = 12.3 Hz, 1H), 4.24-4.40 (m, 3H), 3.96 (s, 3H), 3.12 (dd, J = 19.6, 8.8 Hz, 1H); 2.99 (dd, J = 5.0 Hz, 1H). ^{13}C NMR (67.8 MHz) δ 206.7, 165.5, 161.4, 151.1, 148.5, 140 .5, 136.0, 128.7-127.1, 118.9, 111.7, 111.3, 70.9, 56.4, 53.4, 51.0, 40.0.

Example 3: Synthesis of Compounds of formula III

Overview of Synthesis

The Biaryl PBDs **136, 138** and **140** were obtained by removal of the Troc protecting group from the protected carbinolamines **135, 137** and **139**. For compounds **136** and **138** the deprotection method of Dong *et al*, was employed (Cd/Pb, ammonium acetate buffer), however, this approach could not be applied to the preparation of **140** as this molecule contained a nitro group sensitive to the Cd/Pb couple. In this case a novel deprotection procedure involving the use of tetrabutyl ammonium fluoride was used. The protected biaryl carbinolamines were prepared by the Suzuki reaction, the common 7-iodo substituted protected carbinolamine **134** was exposed to the appropriate boronic acid in the presence of a palladium catalyst, this reaction is of wide scope as over 70 boronic acids are commercially available. The iodo

substituted protected carbinolamine **134** was furnished by Swern oxidation of the primary alcohol **133**. The Swern procedure was particularly effective in this case but other oxidizing agents such as the Dess-Martin reagent, TPAP or pyridine sulphur trioxide complex and DMSO could also be employed. The primary alcohol **133** was afforded by coupling commercially available pyrrolidinemethanol to the Troc protected anthranilic acid chloride obtained by **132** by treatment with oxalyl chloride. The Troc protected acid was in turn prepared by exposing the anthranilic acid **131** to 2,2,2-trichloroethyl chloroformate. Other protecting groups can be used in place of Troc such as Nvoc, Teoc and Fmoc but care must be taken in choosing a protecting group as some groups such as Boc spontaneously form the isatoic anhydride when exposed to oxalyl chloride prior to the coupling step.

The 9-methoxy PBD (**101**) was prepared in an analogous fashion demonstrating the versatility of the approach.

The 8-amino PBD (**151**) was prepared by the removal of a Troc protecting group from the amino substituted protected carbinolamine **150**. The free amine was obtained by removal of an Fmoc protecting group under standard conditions (piperidine/DMF) from the protected carbinolamine **149**. Swern oxidation of the primary alcohol **148** furnished **149** in good yield, the substrate for oxidation reaction was prepared by Fmoc protection of the aniline **147**. Reduction of the nitro compound **146**, with tin chloride furnished the aniline, hydrogenation could not be

employed to reduce the nitro group as the Troc system does not withstand these conditions. The nitro compound **146** was prepared by the coupling of the acid chloride derived from **145** with pyrrolidinemethanol in the presence of base. Finally, the protected anthranilic acid **145** was furnished by exposing the commercially available 4 nitro anthranilic acid **144** to Troc Chloroformate.

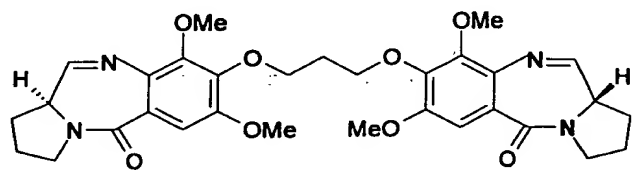
The 8-benzyloxy-7,9-dimethoxy PBD (**143**, UP2022) was prepared by a slightly different approach which does not involve the use of anthranilic acid starting materials but proceeds through 2-nitrobenzoic acid intermediates. The PBD was obtained from the protected carbinolamine **142** by removal of the Troc protecting group under the usual conditions. The protected carbinolamine was furnished by Swern oxidation of primary alcohol **141** which in turn was prepared by selective protection of the amino alcohol **126** as the Troc carbamate by exposure to Troc Chloroformate in the presence of pyridine. The amino alcohol was obtained by reduction of the nitro compound **125** with Raney Nickel and hydrazine (again hydrogenation could not be employed due to the presence of a benzyl group). The nitro alcohol **125** was prepared by coupling pyrrolidine methanol to the requisite 2-nitrobenzoic acid **124**. This nitro benzoic acid was not commercially available and was prepared in four steps from the available syringic acid **87**. Nitration of the ester **122** was proceeded smoothly using Copper nitrate in acetic anhydride, the ester **122** was obtained by standard methods.

The PBDs **96**, **113** and **120** were obtained in an identical fashion from the 2-nitrobenzoic acids **19**, **108** and **115**.

The dimer **90** was prepared in an analogous fashion from the core nitro compound **85**; the core was assembled by joining together two units of the phenol **84** via Mitsonobu etherification. The phenol **84** was derived from syringic acid **83** in a three step synthesis, the crucial step being the nitration of **82** which was performed with 70% nitric acid.

The phenolic PBD **130** was prepared by an analogous route to that used for the synthesis of the PBD **143**, however the requirement to incorporate a phenolic group prompted the use of a different protecting group, Teoc. The free PBD was obtained by treating the Teoc protected carbinolamine **129** with TBAF in warm acetonitrile. The phenol **129** was unmasked by the hydrogenolysis of the benzyloxy moiety of **128** in the presence of the Teoc protecting group (Troc would not survive under these conditions). The benzyloxy compound **128** was obtained by Swern oxidation of the primary alcohol **127** which was prepared by treating the amino alcohol **126** with Teoc chloroformate in the presence of base.

<u>**Example 3(a): Synthesis of the C9/C9'-Dimethoxy PBD Dimer (90, DRH-165) (see Figure 11)**</u>



O-Acetylsyringic acid (82)

A suspension of syringic acid 81 (10.0 g, 50.5 mmol) in acetic anhydride (30.0g, 27.7 mL, 294.1 mmol) was warmed gently until a clear solution was obtained. Fused sodium acetate (0.5g, 6.10 mmol) was added to the solution which was allowed to stir for 16 h at room temperature. The solution was poured into water (100 mL) and stirred thoroughly to ensure hydrolysis of any excess anhydride. Crude *O*-Acetyl-syringic acid was recrystallized from water to afford the product as an off-white powder (11.2 g, 46.7 mmol). H^1 NMR (270 MHz, $CDCl_3$) δ 7.36 (s, 2H), 5.94 (br s, 1H), 3.87 (s, 6H), 2.35 (s, 3H). HRMS calcd for 240.0634, found 240.0637

4-Acetoxy-3,5-dimethoxy-2-nitrobenzoic acid (83)

Fuming nitric acid (5.2 mL) was added, carefully, to a solution of *o*-acetylsyringic acid 82 (11.1 g, 46.2 mmol) in acetic anhydride (33 g, mmol) at 5°C and the reaction mixture was then allowed to stir for 3 h at room temperature. The reaction mixture was poured over ice (300 mL) and the yellow precipitate was collected by filtration, washed with water (3 x 100 mL) and dried *in vacuo* to afford the product as a pale yellow solid (12.4 g). H^1 NMR (270 MHz, $CDCl_3$) δ 7.37 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.39 (s, 3H).

Methyl 3,5-dimethoxy-4-hydroxy-2-nitrobenzoate (84)

A catalytic amount of DMF (5 drops) was added to a solution of oxalyl chloride (6.3 g, 49.8 mmol) and *o*-nitrobenzoic acid **83** (12.4 g, 45.2 mmol) in anhydrous THF (100 mL) and the reaction mixture allowed to stir at room temperature for 16 h. The resulting acid chloride was quenched dropwise with anhydrous methanol (100 mL) at 0 °C. The reaction mixture was treated with potassium carbonate and allowed to stir at room temperature for 3 h. Excess solvent was removed by rotary evaporation at reduced pressure and the residue dissolved in water. The aqueous solution was acidified to pH 8 and the resulting white precipitate was collected by filtration, washed with water (2 x 100 mL) and dried to afford the product as an off-white solid (10.6 g, 83%). H^1 NMR (270 MHz, $CDCl_3$) δ 10.07 (br s, 1H), 7.26 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H).

1′, 3′-Bis(4-carboxy-2,6-dimethoxy-5-nitrophenoxy)propane (85)

Diethylazidodicarboxylate (7.19 g, 41.3 mmol) was added dropwise over 0.5 h to a cooled, stirred solution of the phenol **84** (10.61 g, 41.3 mmol) and TPP (16.24 g, 61.9 mmol) in anhydrous THF (100 mL), and allowed to stir for 1 h. A solution of 1,3-propanediol (1.57g, 20.6 mmol) in THF (30 mL) was added dropwise and the reaction mixture allowed to stir for 16 h. The reaction mixture was then treated with 1N aqueous NaOH (200 mL) and heated at reflux for 3 h. Excess solvent was removed by rotary evaporation under reduced pressure to afford an aqueous suspension which was extracted with EtOAc (3 x 300 mL). The aqueous extract was acidified with concentrated HCl and the precipitate collected by

vacuum filtration. The precipitate was suspended in water (500 mL) and after stirring for 10 minutes, the suspension was filtered to afford the product as an orange solid (6.11 g, 60%). H^1 NMR (270 MHz, $CDCl_3$) δ 7.32 (s, 2H), 4.36 (t, 4H,), 3.92 (s, 6H), 3.90 (s, 6H), 2.20 (t, 2H).

(2*S*)-1,1'-[[(propane-1,3-diyl)dioxy]bis[2-nitro-3,5-dimethoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethylpyrrolidine] (86)

A catalytic amount of DMF (3 drops) was added to a solution of the acid 85 (6.1g, 12.4 mmol) and oxalyl chloride (2.37 mL, 3.45 g, 27.2 mmol) in anhydrous DCM (60 mL) and the reaction mixture allowed to stir at room temperature for 16 h. The resulting acid chloride was added dropwise over 0.5 h to a stirred solution of TEA (6.26 g, 61.8 mmol) and pyrrolidinemethanol (2.75 g, 27.2 mmol) in anhydrous DCM (60 mL) at -10°C. The reaction mixture was then allowed to stir at room temperature for 6 h. The reaction mixture was washed with 1N HCl (3 x 100 mL), water (3 x 100 mL), saturated $NaHCO_3$ (3 x 100 mL), brine (3 x 100 mL) and dried over $MgSO_4$. Removal of excess solvent by rotary evaporation under reduced pressure afforded the product as a yellow glass (8.25 g, 11.9 mmol). H^1 NMR (270 MHz, $CDCl_3$) δ 6.66 (s, 2H), 4.32-4.26 (m, 6H), 3.98 (s, 6H), 3.90 (s, 6H), 3.86-3.67 (m, 4H), 3.41-3.27 (m, 4H), 2.23-2.12 (m, 2H), 2.11-1.72 (m, 8H).

(2*S*)-1,1'-[[(propane-1,3-diyl)dioxy]bis[2-amino-3,5-dimethoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethylpyrrolidine] (87)

Hydrazine (3.45 g, 107.9 mmol) was added dropwise to a solution of **86** (1g, 1.45 mmol) in anhydrous methanol (40 mL) heated at reflux over Raney nickel (5 g, slurry). Heating was continued for a further 3 h after which time the reaction mixture was allowed to cool and filtered through celite to remove excess Raney nickel. The filtrate was evaporated to dryness and dissolved in DCM (200 mL) and the organic solution washed with water (2 x 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. Filtration and evaporation of excess solvent *in vacuo* afforded the product as a pink glass (5.59 g, 8.9 mmol, 98%). H^1 NMR (270 MHz, $CDCl_3$) δ 6.54 (s, 2H), 4.35 (br s, 2H), 4.29 (t, 4H), 3.85 (s, 3H), 3.83-3.46 (m, 14H), 2.20-2.13 (m, 2H), 1.97-1.66 (m, 8H).

(2*S*)-1,1'-[[(propane-1,3-diyl)dioxy]bis[2-(2',2',2'-trichloroethoxycarbonyl)amino-3,5-methoxy-1,4-phenylene)carbonyl]]bis[2-(hydroxymethylpyrrolidine] (88)

A solution of 2,2,2-trichloroethylchloroformate (1.45 g, 6.86 mmol, 1.9 eq) in dry DCM (10 mL) was added dropwise over the space of 0.5 h to a solution of **87** (2.28 g, 3.6 mmol) and pyridine (1.14 g, 14.4 mmol, 4 eq) in dry DCM (50 mL) and allowed to stir for 16 h at room temperature. The reaction mixture was diluted with DCM (200 mL) and washed with 1N HCl (3 x 200 mL), H_2O (3 x 200 mL), brine (2 x 300 mL) and dried over anhydrous $MgSO_4$. Purification by flash chromatography (silica gel, EtOAc) afforded the product as a pale yellow glass (1.43 g). H^1 NMR (270

MHz, $CDCl_3$) Rotamers δ 9.21 and 8.40 (2 x br s, 2H), 6.49 and 6.54 (2 x s, 2H), 5.08-3.59 (m, 26H), 3.33-3.30 (m, 4H), 2.04-1.69 (m, 10H).

1,1'-[[Propane-1,3-diyl)dioxy]bis[(11*S*,11a*S*)-10-(2',2',2'-trichloroethoxycarbonyl)-11-hydroxy-7,9-dimethoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one. (89)

A solution of dry DMSO (14.9 mmol, 1.17g, 1.06 mL) in dry DCM (5 mL) was added dropwise over 20 minutes to a stirred solution of oxalyl chloride in DCM (7.38 mmol, 3.69 mL of a 2N solution in DCM) under a nitrogen atmosphere at -45° C. After stirring for an additional 15 minutes, a solution of 88 (2.58 g, 2.63 mmol) in dry DCM (5m L) was added dropwise over 45 minutes at -45° C and stirred for 45 minutes at -45° C. TEA (2.12 g, 21.0 mmol) was added dropwise over 30 minutes and stirred for a further 15 minutes. The reaction mixture was allowed to warm to room temperature, and diluted with water (100 mL). The organic layer was washed with 1N HCl (3 x 100 mL), water (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the product as a yellow glass (0.73 g). H^1 NMR (270 MHz, $CDCl_3$) δ 7.06 (s, 2H), 5.61 (dd, 2H, *J* = 3.39, 9.9 Hz), 4.74 (d, 2H, *J* = 11.72 Hz), 4.62 (d, 2H, *J* = 11.91 Hz), 4.29-4.21 (m, 6H), 3.97-3.46 (m, 16H), 2.28-2.01 (m, 10H).

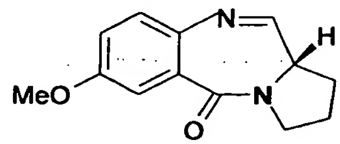
Preparation of 10% Cd/Pb couple

Yellow lead oxide (litharge, 1.8 g, 4.9 mmol) was dissolved in warm 50% aq. AcOH (50 mL) and the solution was slowly added to a vigorously stirred suspension of Cd dust (Aldrich, 100 mesh, 5.46 g, 49 mmol) in deionised water (100 mL). The Cd darkened as Pb deposited on its surface, and formed clumps that were gently broken up with a glass rod. The dark non-pyrophoric Cd/Pb couple was filtered, washed with water, acetone, crushed and dried prior to storage and use.

1,1'-[[Propane-1,3-diyl)dioxy]bis[(11a*S*)-7,9-dimethoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one. (90)

Cadmium/lead couple (3.8 mmol Cd, 0.47 g of Cd\Pb couple) was added to a vigorously stirred solution of 89 (0.76 g, 0.8 mmol) in THF (10 mL) and 1N NH_4OAc (10 mL) and stirring continued for 2.5 h. The reaction mixture was diluted with DCM (150 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* afforded the product as a yellow glass (0.32 g, 0.55 mmol, 71%). H^1 NMR (270 MHz, $CDCl_3$) mixture of C11/C11'R/S carbinolamines δ 7.08 (s, 2H), 5.53 (br s, 2H), 5.38 (br s, 2H), 4.90 (d, 2H, J = 9 Hz), 4.79 (d, 2H, J = 9 Hz), 4.38-3.54 (m, 22H), 2.27-1.79 (m, 10H). MS (FAB) m/e (relative intensity) 594 (M+2, 27%), 593 (M+1, 69%)

Example 3(b): Synthesis of the C7-Methoxy PBD (96, DRH-271) (see Figure 12)



N-(3-Methoxy-2-nitrobenzoyl)pyrrolidin-2-methanol (92)

A catalytic amount of DMF (2 drops) was added to a stirred solution of 3-methoxy-2-nitro-benzoic acid **91** (5.01 g, 25.4 mmol) and oxalyl chloride (3.54 g, 27.9 mmol) in dry $CHCl_2$ (50 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight, before being used directly in the preparation of **92**. A solution of the acid chloride in anhydrous $CHCl_2$ (50 mL) was added dropwise over 1 h to a vigorously stirred solution of pyrrolidinemethanol (2.57 g, 25.4 mmol) and TEA (6.42 g, 63.6 mmol) in anhydrous $CHCl_2$ (50 mL) under a nitrogen atmosphere at 0°C and allowed to stir overnight at room temperature. The reaction mixture was washed with 1N HCl (1 x 100 mL), H_2O (3 x 100 mL) and brine (3 x 100 mL). The organic layer was dried over anhydrous $MgSO_4$, and evaporation of the solvent afforded a brown oil (6.37 g, 22.7 mmol, 89%).

N-(2-Amino-3-Methoxybenzoyl)pyrrolidin-2-methanol (93)

Hydrazine hydrate (4.37 g, 136.4 mmol) was added dropwise to a solution of **92** (6.37 g, 22.7 mmol) in gently refluxing methanol (100 mL) over Raney nickel (2.4 g, slurry). The resulting vigorous evolution of hydrogen gas subsided after approximately 10 mins and the reaction was deemed to be complete by TLC after 2

h. The reaction mixture was filtered through celite and the solvent evaporated. Distilled water (100 mL) was added to the residue, and the aqueous mixture was extracted with EtOAc (3 x 100 mL) and washed with H_2O (3 x 100 mL) and brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a brown glass (5.49 g, 21.8 mmol) as a single spot by TLC.

N-(3-Methoxy-2-((2',2',2'-trichloroethoxy)carbonylaminobenzoyl)pyrrolidin-2-methanol (94)

A solution of 2,2,2-trichloroethyl chloroformate (4.61 g, 21.8 mmol) in distilled dichloromethane (50 mL) was added dropwise over 0.5 h to a stirred solution of the substrate, 93 (5.46 g, 21.8 mmol) and anhydrous pyridine (3.44 g, 43.5 mmol) in distilled dichloromethane (100 mL) at 0°C. The reaction mixture was allowed to stir for 2.5 hours at which time TLC showed reaction to be complete. The reaction mixture was diluted with anhydrous DCM (100 mL) and washed with 1N HCl (2 x 200 mL), H_2O (200 mL), brine (200 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded a brown oil which was purified by flash column chromatography eluting with EtOAc to afford the product as a yellow solid (6.14 g, 14.4 mmol); ^1H NMR (270 MHz, $CDCl_3$) δ 1.75-2.25 (m, 4H), 3.4-3.75 (m, 2H), 3.8 (s, 3H), 3.85-4.2 (m, 2H), 4.40 (m, 1H), 4.73-4.86 (m, 2H), 6.86-6.97 (m, 2H), 7.85 (br d, 1H, J = 9Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.9, 155.6, 152.4, 128.2, 127.8, 123.6, 116.0, 113.0, 95.4, 74.4, 65.9, 60.9, 55.7, 51.0, 28.3, 24.9.

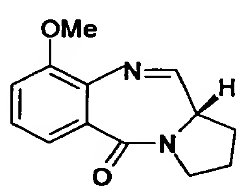
(11*S*,11a*S*)-10-(2',2',2'-trichloroethoxy)carbonyl-7-methoxy-11-hydroxy-1,2,3,10,11,-11a-hexahydro-5*H*-pyrrolo[2,1-c][1,4]benzodiazepin-5-one.(95)

Anhydrous DMSO (3.14 g, 40.2 mmol) in dry DCM (25 mL) was added dropwise over 5 mins to a stirred solution of oxalyl chloride (2.53 g, 9.96 mL of a 2 N solution in DCM) under a nitrogen atmosphere at -50°C. After stirring for 5 minutes, the substrate **94** (6.03 g, 14.2 mmol) in dry DCM (25 mL) was added dropwise over 45 mins to the reaction mixture, which was then allowed to stir for a further 45 mins at -50°C after the addition of the substrate. Dry TEA (5.72 g, 56.64 mmol) was added dropwise to the mixture over 0.5 h and the reaction mixture allowed to stir for a further 15 minutes. The reaction mixture was left to warm to room temperature and diluted with H_2O (100 mL). The organic phase was washed with 1N HCl (2 x 200 mL), H_2O (2 x 200 mL), brine (2 x 200 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford a yellow oil (6.68 g). The oil was subjected to flash chromatography with EtOAc as eluent to afford the product as a yellow solid (5.87 g, 13.9 mmol); ^1H NMR (270 MHz, $CDCl_3$) δ 1.99-2.14 (m, 4H), 3.45-3.77 (m, 2H), 3.85 (s, 3H), 4.19 (br s, 1H), 4.28 (d, 1H, J = 11.91 Hz), 5.14 (d, 1H, J = 11.91 Hz), 5.66 (d, 1H, J = 9.71 Hz), 6.97-7.02 (m, 1H), 7.23-7.27 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) d 166.8, 159.1, 154.7, 134.3, 131.5, 129.9, 126.6, 118.106, 112.5, 112.3, 95.0, 86.0, 75.2, 75.1, 59.8, 55.7, 46.7, 46.4, 28.7, 23.0, 21.0, 14.2.

7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (96)

10% Cd/Pb couple (2.50 g, 20 mmol Cd) was added to a rapidly stirring solution of 95 (1.71 g, 4.03 mmol) in a mixture of THF (30 mL) and 1N NH4OAc (30 mL). Upon addition, the solution turned cloudy and after 2 h TLC showed the reaction to be complete. The reaction mixture was diluted with EtOAc (150 mL) and dried over anhydrous MgSO4. The solids were filtered and rinsed with EtOAc (50 mL). Removal of excess solvent by rotary evaporation under reduced pressure afforded the product as a yellow solid (0.84 g, 3.6 mmol, 90%)

Example 3(c): Synthesis of the C7-Methoxy PBD (101, AG/140)(see Figure 13)



3-methoxy-2-(2',2',2'-trichloroethoxycarbonylamino)benzoic acid (98)

2-amino-3-methoxybenzoic acid 97 (1 g, 6.0 mmol) and pyridine (0.97 mL, 12.0 mmol) were dissolved in dry dichloromethane (30 mL). The resulting mixture was cooled and Troc-Cl (0.9 mL, 6.6 mmol) was added drop wise. The reaction mixture was allowed to stir overnight at room temperature, then washed with HCl (1N, 50 mL), water (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield 1.42 g of crude product, which was used in the next step without further purification.

N-(3-methoxy-2-(2',2',2'-trichloroethoxycarbonylamino)benzoyl)-pyrrolidine-2-methanol (99)

Oxalyl chloride (0.57 mL, 6.58 mmol) together with 2 drops of dry DMF was added to a solution of the crude product obtained from the previous reaction in dry dichloromethane (20 mL). After initial strong effervescence, the mixture was allowed to stir at room temperature overnight. The resulting acid chloride was added drop wise, over 30 minutes to a solution of 2*S*-(+)-pyrrolidinemethanol (0.66 g, 6.58 mmol) and TEA (2.1 mL, 14.95 mmol) in dry dichloromethane (20 mL) at -16°C. Once coupling was complete the reaction mixture was diluted with ethyl acetate (20 mL), and washed with 1N HCl (2 x 25 mL), satd. aqueous $NaHCO_3$ (2 x 25 mL), water (25 mL) and brine (25 mL). The organic layer was then dried over $MgSO_4$ and evaporated to give a yellow oil. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 50/50) to afford 0.54 g, of a pale yellow oil: ^1H NMR (270 MHz, $CDCl_3$) d 1.6 - 1.8 (m, 1H); 1.81 - 2.0 (m, 2H); 2.02 - 2.21 (m, 1H); 3.4 (m, 1H); 3.6 (m, 2H); 3.86 (m, 4H); 4.22 (dd, J = 5.1, J = 12.3 Hz, 1H); 4.72 (d, J = 12 Hz, 1H); 4.79 (d, J = 12 Hz, 1H); 4.86 (m, 1H); 6.91 (s, 1H); 6.94 (s, 1H); 7.2 (dd, J = 7.5, J = 8.4 Hz, 1H); 7.36 (bs, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.6; 28.8; 50.7; 55.9; 61.3; 66.5; 74.8; 75.3; 111.7; 111.9; 119.1; 122.3; 126.3; 132.9; 152.7; 170.3 IR (Nujol): cm^{-1} 3410, 2969, 1738, 1613, 1583, 1514, 1429, 1268, 1218, 1109, 1079, 1049, 809, 759. MS: m/e (relative intensity) 425 (M+, 10), 394 (20), 323 (30), 276 (35), 245 (100), 176 (100), 149 (45), 120 (40), 106 (20), 77 (30), 70 (100). HRMS Calculated for $C_{16}H_{19}Cl_3N_2O_5$: 424.0357. Found: 424.0359. $[a]^{25}_D = -45.1°$

(c = 0.63, $CHCl_3$).

(11S,11aS)-11-hydroxy-9-methoxy-10-N-(2',2',2'-trichloroethoxycarbonyl)-1,2,-3,10,11,11a-hexahydro-5H-pyrrolo [2,1-c][1,4] benzodiazepin-5-one (100)

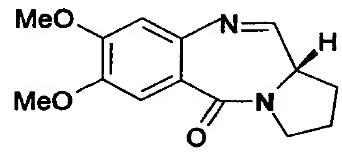
A solution of DMSO (0.46 ml, 6.63 mmol) in of dry dichloromethane (10 mL) was added drop wise over 30 minutes to a solution oxalyl chloride (3.30 mmol,) in dry dichloromethane (11.65 mL) at -40°C. The mixture was allowed to stir for a further 30 minutes, a solution of 99 (1 g, 2.37 mmol) in dichloromethane (15 mL) was then added drop wise over 1hour. Following the end of addition the mixture was allowed to stir at -45°C for 60 minutes, then a solution of TEA (1.31 mL) in dichloromethane (6 mL) was added drop wise and the mixture was allowed to warm to room temperature. The reaction mixture was washed with water (50 mL), 1N HCl (2 x 25 mL), satd. aqueous $NaHCO_3$ (2 x 25 mL), and brine (50 mL). The organic solution was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (silica gel EtOAc/petroleum ether 1/1) to give a colourless oil (0.64 g, 63%): ^1H NMR (270 MHz, $CDCl_3$) δ 2.01 - 2.15 (m, 4H); 3.43 - 3.58 (m, 2H); 3.73 (m, 2H); 3.83 (s, 3H); 4.35 (d, J = 12, 1H); 4.98 (d, J = 12, 1H); 5.66 (dd, J =3.8, J = 9.6 Hz, 1H); 7.02 (dd, J = 2.2, J = 7.5 Hz, 1H); 7.35 (m, 2H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.0; 28.6; 46.2; 56.1; 59.9; 75.3; 86.2; 94.8; 113.4; 120.2; 123.1; 129.4; 134.9; 154.7; 155.4; 166.7. IR (Nujol): cm^{-1} 3291, 2924, 1724, 1616, 1580, 1463, 1318, 1278, 1075, 945, 812, 739. MS: m/e (relative intensity) 422 (M-1, 40), 387 (3), 275 (10), 245 (15), 217 (10), 176 (100),

150 (8), 120 (6), 70 (95). HRMS Calculated for $C_{16}H_17C_13N_2O_5$: 422.0202. Found: 422.0203. $[a]^{25}_D$= + 136.5° (c = 0.19, CHCl3).

(11aS)-9-methoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (101)

Finely ground Cd/Pb couple (1.02 g). was added in small portions to a stirred solution of **100** (0.64 g, 1.51 mmol) in THF (10 mL) and 1M NH_4OAc (10 mL). The reaction was followed by TLC (EtOAc), when no more starting material was observed, the mixture was poured into ethyl acetate (200 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield the product as a pale yellow oil (0. 28 g, 80%): ^1H NMR (270MHz, $CDCl_3$) δ 2.15 (m, 4H); 3.52 (m, 2H); 3.87 (s, 3H); 5.15 (m, 1H); 6.8 - 7.2 (m, 3H); 7.8 (d, J = 4.7 Hz, 1H, imine H11). IR (Nujol): cm^{-1} 3373, 2975, 1621, 1576, 1440, 1419, 1250, 1075, 750. MS: m/e (relative intensity) 230 ($M^{+\cdot}$, 100), 215 (45), 201 (20), 187 (5), 160 (5), 146 (4), 133 (20), 105 (10), 76 (25), 70 (45), 63 (3), 51 (3). HRMS Calculated for $C_{13}H_14N_2O_2$: 230.1055. Found: 230.1055. $[a]^{25}_D$ = + 455.3° (c = 0.6, $CHCl_3$).

Example 3(d): Synthesis of the 7,8-Dimethoxy PBD (106, AG/105) (see Figure 14)



4,5-dimethoxy-2-(2',2',2'-trichloroethoxycarbonylamino)benzoic acid (103)

A solution of Troc-Cl (0.76 ml, 5.56 mmol) in dry dichloromethane (10 mL) was added dropwise to 2-amino-4,5-dimethoxybenzoic acid 102 (1 g, 5.1mmol) and pyridine (0.82 ml, 10.1 mmol) in dry dichloromethane (20 ml) at 0° C. The reaction mixture was allowed to stir overnight at room temperature and then washed with dilute HCl (1N, 2 x 2 5 ml), water (2 x 25 ml) and brine (20 ml). The organic phase was dried over $MgSO_4$ and evaporated to yield of crude product (1.6 g), which was used in the next step without further purification.

N-(4,5-dimethoxy-2'-(2",2",2"-trichloroethoxycarbonylamino)benzoyl)-pyrrolidine-2-methanol (104)

Oxalyl chloride (0.38 mL, 4.33 mmol) was added to the crude Troc-protected anthranilic acid, prepared in the previous reaction, together with 2 drops of dry DMF in dry dichloromethane (30 mL). After initial strong effervescence, the mixture was allowed to stir at room temperature overnight. The resulting acid chloride was added dropwise, over 30 minutes, to a solution of 2*S*-(+)-pyrrolidinemethanol (0.44 g, 4.33 mmol) and TEA (1.37 ml, 9.85

mmol) of dry dichloromethane (15 mL) at -16°C. The reaction mixture was diluted with ethyl acetate (20 mL), and washed with dilute HCl (1N, 2 x 30 mL), satd. aqueous $NaHCO_3$ (2 x 30 mL), water (30 mL) and brine (30 mL). The organic layer was then dried over $MgSO_4$ and evaporated to give a yellow oil. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 50/50) to yield the product (1.2 g, 70%) as a pale yellow oil: ^1H NMR (270 MHz, $CDCl_3$) δ 1.75 (m, 2H); 1.92 (m, 1H); 2.17 (m, 1H); 3.53 (m, 2H); 3.72 (m, 1H); 3.86 (s, 3H); 3.93 (s, 3H); 4.19 (m, 1H); 4.43 (m, 1H); 4.77 (d, *J* = 12 Hz, 1H); 4.85 (d, *J* = 12 Hz, 1H); 6.85 (s, 1H); 7.69 (s, 1H); 9.08 (bs, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.1; 28.2; 51.4; 56.0; 56.4; 60.8; 65.9; 74.4; 95.3; 104.7; 110.7; 116.3; 130.8; 144.4; 151.0; 152.1; 170.4. MS: m/e (relative intensity) 454 (M-1, 5), 356 (3), 306 (10), 275 (5), 206 (100), 179 (15), 150 (10), 136 (3), 70 (45). HRMS Calculated for $C_{17}H_{21}Cl_3N_2O_6$: 454.0465. Found: 454.0464. $[a]^{25}_D$= - 72.2° (*c* = 0.18, CHCl3).

(11S,11aS)-7,8-dimethoxy-11-hydroxy-10-N-(2′,2′,2′-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo [2,1-c][1,4] benzodiazepin-5-one (105)

A solution of DMSO (0.9 ml, 12.9 mmol) in dry dichloromethane (15 mL) was added dropwise over 30 minutes to a solution of oxalyl chloride (6.4 mmol) of dry dichloromethane (15 mL) keeping the temperature below -40°C. The reaction mixture was allowed to stir for further a 30 minutes at which point a solution of 104 (2.1 g, 4.61 mmol) in dichloromethane (35 mL) was added drop wise over 1 hour. After addition of the substrate the reaction

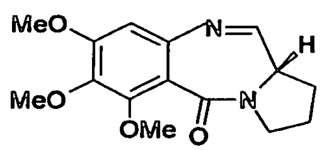
mixture was allowed to stir at -45°C for 60 minutes, and then treated with a solution of TEA (2.56 mL) in of dichloromethane (10 mL) were added drop wise and the mixture was allowed to warm to room temperature. The reaction mixture was washed with water (75 mL), dilute HCl (1N, 75 mL), water (75 mL), brine (75 mL) dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (EtOAc/petroleum ether 40/60) to give a colourless oil (1.19 g, 57%): ^1H NMR (270 MHz, $CDCl_3$) δ 2.04 (m, 2H); 2.11 (m, 2H); 3.47 - 3.59 (m, 2H); 3.68 - 3.75 (m, 1H); 3.91 (s, 3H); 3.94 (s, 3H); 4.21 (d, J = 12.1 Hz, 1H); 4.43 (d, J = 4.76 Hz, 1H); 5.27 (d, J = 12.1 Hz, 1H); 5.65 - 5.7 (dd, J = 4.58, J = 9.71 Hz, 1H); 6.82 (s, 1H); 7.26 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.1; 28.6; 46.4; 56.0; 56.1; 60.0; 74.9; 86.4; 95.1; 110.3; 112.7; 125.6; 148.6; 150.8; 154.5; 167.0. MS: m/e (relative intensity) 452 (M-1, 30), 424 (7), 354 (10), 276 (25), 206 (100), 180 (10), 150 (10), 70 (100). HRMS Calculated for $C_{17}H_{19}Cl_3N_2O_6$: 452.0308. Found: 452.0309. $[a]^{25}_D = + 104.7°$ (c = 0.27, $CHCl_3$).

(11aS)-7,8-dimethoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (106, AG/105)

Finely ground Cd/Pb couple (3.12 g) was added portion wise to a solution of **105** (1 g, 2.2 mmol) THF (10 mL) and NH_4OAc (1M, 10 mL). The reaction was followed by TLC (EtOAc), when no starting material was present, the mixture was poured into ethyl acetate (400 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield the crude product, which was purified by flash chromatography (EtOAc) to give of the pure compound as a pale

yellow oil (0.45 g, 78%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.08 (m, 2H); 2.29 (m, 2H); 3.53 - 3.63 (m, 1H); 3.72 (m, 1H); 3.79 - 3.85 (m, 1H); 3.93 (s, 3H); 3.96 (s, 3H); 6.82 (s, 1H); 7.52 (s, 1H); 7.68 (d, *J* = 4.4, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.2; 29.6; 46.7; 53.7; 56.0; 56.1; 109.4; 111.2; 140.7; 147.5; 151.3; 162.5; 164.6. IR (Nujol): cm^{-1} 3000-2800, 1601, 1450, 1434, 1500, 1453, 1263, 1217, 1010, 908, 735. MS: m/e (relative intensity) 260 (M+, 100), 245 (50), 231 (25), 217 (10), 191 (20), 164 (25), 136 (20), 121 (5), 93 (8), 70 (10). HRMS Calculated for $C_{14}H_16N_2O_3$: 260.1160. Found: 260.1161. $[a]^{25}_{D}$ = + 1004.7° (c = 0.17, CHCl3).

<u>Example 3(e): Synthesis of the 6,7,8-Trimethoxy PBD (113, DRH-NA7)(see Figure 15)</u>



2,3,4-Trimethoxy-6-nitrobenzoic acid (108)

2,3,4-trimethoxybenzoic acid **107** (25 g, 117.8 mmol) was added portionwise to a stirred solution of 70% nitric acid at 0°C for 30 minutes. The reaction mixture was poured into cold water (1250 mL) and stirring was continued for 30 minutes. The reaction mixture was extracted with EtOAc (2 x 200 mL) and the combined organic layers were washed with brine (2 x 200 mL) and dried over anhydrous MgSO4. Evaporation of excess solvent *in vacuo* afforded the product as a pure white crystalline solid (18.67 g, 60%): R_f = 0.5 (silica, EtOAc); IR (nujol) 2922, 1713, 1618, 1570, 1504, 1464, 1401, 1308, 1246, 1168, 1111, 1028, 920,

852, 789, 773, 728, 689 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.76 (1H, s), 4.0 (3H, s), 3.95 (3H, s), 3.90 (3H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.0, 153.2, 150.1, 147.79, 139.6, 120.8, 103.6, 62.2, 61.1, 56.5; MS (EI) m/z 258 (M+1), 240, 214.

N-(2-Nitro-4,5,6-trimethoxybenzoyl)pyrrolidine-2-methanol (109)

A catalytic quantity of DMF (2 drops) was added to a stirred solution of **108** (10 g, 38.9 mmol) and oxalyl chloride (5.87 g, 46.2 mmol) in dry $CHCl_2$ (100 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight, and the product was used directly in the next stage of the reaction. The newly formed acid chloride was added dropwise to a stirred solution of pyrrolidinemethanol (3.92 g, 38.8 mmol) and anhydrous triethylamine (12.4 mL, 9.8 g, 97.0 mmol) in anhydrous DCM (50 mL) at 0°C under nitrogen. Once the addition was complete, the reaction mixture was left to warm to room temperature and left to stir overnight. The reaction mixture was washed with 1N HCl (100 mL), water (100 mL), and brine (2 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford **109** (12.1 g, 91%) as a pale yellow oil: R_f = 0.39 (silica, EtOAc); $[a]^{21.9}_D$ +135° (c = 0.1, DCM); IR (neat) 3400, 3105, 2947, 2878, 1652, 1568, 1538, 1455, 1348, 1250, 1195, 1115, 975, 922, 849, 822, 792, 758, 733, 646 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.59 (1H, s), 4.46 (2H, d, J = 2.93 Hz), 4.07 (3H, s), 4.03 (3H, s), 4.01 (3H, s), 3.89 (3H, t), 3.45-3.29 (2H, m), 2.24-2.17 (2H, m), 2.00-1.84 (2H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$, rotamers) δ 165.7, 165.1, 153.3, 149.2, 148.1, 138.8, 122.5, 104.1, 66.4, 65.5, 62.4, 62.3, 61.3, 56.6, 49.2, 49.0, 28.7 24.3; MS (EI) m/z

341 (M+1), 324, 309, 293, 277, 264, 254.

N-(2-Amino-4,5,6-trimethoxybenzoyl)pyrrolidine methanol (110)

Hydrazine hydrate (5.67 g, 177.2 mmol) was added dropwise to a solution of **109** (12.1 g, 35.47 mmol) in gently refluxing methanol (142 mL) over Raney nickel (3.45 g, slurry). The resulting vigorous evolution of hydrogen gas subsided after approximately 10 mins and the reaction was deemed to be complete by TLC after 3 h. The reaction mixture was filtered through celite and the solvent evaporated. Distilled water (200 mL) was added to the residue, and the aqueous mixture was extracted with DCM (2 x 100 mL) and the combined organic phase washed with H_2O (3 x 100 mL) and brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded **110** (11.24 g) as a yellow oil. R_f = 0.14 (silica, EtOAc); $[a]^{21.8}{}_D$ = +100° (c = 0.1, DCM); IR (neat) cm^{-1} 3355, 2940, 2879, 2843, 1614, 1498, 1463, 1428, 1410, 1365, 1339, 1240, 1199, 1123, 1078, 1039, 997, 915, 817, 731, 646; ^1H NMR (270 MHz, $CDCl_3$) δ 6.10 (1H, s), 4.37 (2H, d, J = 3.67 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.86 (3H, s), 3.67 (2H, t), 2.17-2.02 (2H, m), 1.87-1.82 (2H, m) ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 168.8, 154.7, 150.9, 149.6, 140.6, 133.8, 95.8, 66.5, 61.8, 61.4, 61.3, 61.1, 49.2, 28.6, 24.4; MS (EI) m/z 310 (M^+), 294, 279, 229, 210, 194, 180, 149, 124, 102, 83, 70, 57.

N-(2-[2′,2′,2′-Trichloroethoxycarbonylamino]-4,5,6-trimethoxybenzoyl)pyrrolidine-2-methanol (111)

A stirred solution of **110** (11.24 g, 36.3 mmol) in DCM (150 mL)

and pyridine (5.86 mL, 5.73 g, 72.5mmol) was treated dropwise with 2,2,2-trichloroethyl chloroformate (5 mL, 7.61 g, 35.9 mmol) in DCM (50 mL) under a nitrogen atmosphere at 0° C. One hour after the addition of 2,2,2-trichloroethyl chloroformate, the reaction mixture was diluted with DCM (100 mL) and washed with 1N HCl (100 mL), water (2 x 150 mL), brine (2 x 100 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford **111** (15.44 g, 88%) as a clear brown oil: R_f = 0.44 (silica, EtOAc); IR (neat) cm^{-1} 3437, 2948, 1738, 1628, 1497, 1458, 1422, 1397, 1238, 1115, 1027, 1008, 823, 760, 624; ^1H NMR (270 MHz, DMSO) δ 6.82 (1H, s), 5.06 (2H, s), 4.04 (2H, d, J = 6.83 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.79 (3H, s), 3.67 (2H, t), 2.00-1.97 (2H, m), 1.96-1.88 (2H, m) ^{13}C NMR (67.8 MHz, DMSO) δ 164.2, 153.5, 149.6, 139.6, 129.4, 121.3, 96.2, 73.9, 61.4, 60.9, 58.7, 56.2, 47.9, 27.5, 23.7; HRMS (FAB) calcd for $C_{18}H_{2}3N_2O_7Cl_3$ ($M^{+\cdot}$) 484.0571, found 484.0944.

6,7,8-Trimethoxy-10-(2',2',2'-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (112)

A solution of oxalyl chloride in DCM (22.3 mL of a 2N solution, 44.7 mmol) diluted with anhydrous DCM (42 mL) at -45°C was treated dropwise with a solution of anhydrous DMSO (6.39 mL, 90.2 mmol) in anhydrous DCM (16.24 mL) over a period of 15 minutes. The reaction mixture was stirred at -45°C for 15 minutes and treated with a solution of **111** (15.44 g, 31.7 mmol) in dry DCM (34.3 mL) and stirred at -45° C for 45 minutes. Triethylamine (17.7 mL, 127.1 mmol) was added dropwise to the reaction mixture over 0.5 h, and then allowed to stir for a further 15 minutes.

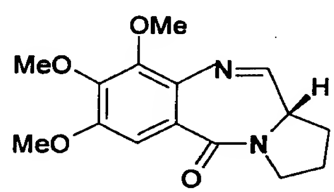
The reaction mixture was allowed to warm to room temperature and diluted with water (100 mL). The organic layer was washed with 1N HCl (200 mL), water (200 mL), brine (200 mL) and dried ($MgSO_4$). The reaction mixture was evaporated and purified by flash column chromatography (EtOAc) to afford the product **112** (8.27 g, 54%) as a clear yellow glass: R_f = 0.48 (silica, EtOAc); $[a]^{22.2}{}_D$ +190° (*c* 0.15, DCM); IR (neat) cm^{-1} 3262, 2979, 2943, 2885, 1732, 1613, 1493, 1456, 1399, 1372, 1334, 1299, 1264, 1244, 1201, 1118, 1059, 1014, 969, 926, 888, 838, 784, 756, 720, 693, 624; ^1H NMR (270 MHz, $CDCl_3$) δ 6.64 (1H, s), 5.58 (1H, s), 5.31 (1H, s), 4.34 (1H, d, *J* = 19.78 Hz), 4.15-4.00 (1H, m), 3.95 (3H, s), 3.91 (3H, s), 3.90 (3H, s), 3.77 (2H, t), 3.55 (1H, t), 2.17-2.14 (2H, m), 2.14-2.10 (2H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 163.49, 154.32, 152.30, 142.69, 129.51, 121.16, 109.35, 95.20, 85.63, 62.30, 61.36, 60.48, 56.09, 45.56, 28.44, 22.85; MS (EI) m/z 485 (M+1), 467, 398, 384, 350, 291, 254, 236, 222, 194, 131, 102, 82, 70, 57.

6,7,8-Trimethoxy-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (113)

10% Cd/Pb couple (2.57 g, 20.6 mmol Cd) was added to a stirred solution of **112** (2.00 g, 4.1 mmol) in THF (20 mL) and 1N NH_4OAc buffer (20 mL) and left at room temperature for 4 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (2 x 100 mL). The organic layer was washed with brine (2 x 100 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give **113** (0.76 g, 64%) as a yellow glass: R_f = 0.1 (silica, EtOAc); $[a]^{20.7}{}_D$ = +505° (*c* = 0.1, DCM); IR (neat) cm^{-1} 3339, 2976,

2939, 1614, 1455, 1428, 1392, 1359, 1275, 1245, 1203, 1113, 1052, 1035, 1000, 926, 804, 751, 665; ^{1}H NMR (270 MHz, $CDCl_3$) δ (1H, d, J = 4.39 Hz), 6.61 (1H, s), 6.14 (1H, d, J = 8.24 Hz), 4.36 (1H, d, J = 8.79 Hz), 4.01 (3H, s), 3.98 (3H, s), 3.84 (3H, s), 3.48-3.46 (2H, m) 2.26-2.23 (2H, m), 2.16-1.93 (2H, m); HRMS (FAB) calcd for $C_{15}H_18N_2O_4$ (M+1) 290.1266, found 290.1208.

<u>Example 3(f): Synthesis of the 7,8,9-Trimethoxy PBD (120, DRH-69) (see Figure 16)</u>



3,4,5-Trimethoxy-2-nitrobenzoic acid (115)

Methyl 3,4,5-trimethoxy-2-nitrobenzoic **114** (24.37 g, 89.9 mmol) was added to a 5% solution of KOH (18 g) in MeOH (357 mL). The mixture was heated at reflux for 50 minutes. Evaporation of the solvent afforded a grey residue, which was dissolved in H_2O (200 mL) The resulting alkaline solution was acidified to pH1 with concentrated HCl, and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was washed with H_2O (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent afforded a pure white crystalline solid (20.67 g, 80.4 mmol): ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.9 (s, 3H), 4.0 (s, 3H), 4.1 (s, 3H), 7.4 (s, 1H), 12.4 (br s, 1H).

N-(2-Nitro-3,4,5-trimethoxybenzoyl)pyrrolidine-2-methanol (116)

A catalytic amount of DMF (2 drops) was added to a stirred solution of **115** (2.57 g, 10 mmol) and oxalyl chloride (1.40 g, 11 mmol) in dry CH_2Cl_2 (40 mL) under an inert atmosphere. The reaction mixture was allowed to stir overnight, the resulting solution of the acid chloride, (2.76 g, 10 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise over 1 h to a vigorously stirred solution of pyrrolidinemethanol (1.11 g, 11 mmol) and TEA (2.52 g, 25 mmol) in anhydrous CH_2Cl_2 (40 mL) under a nitrogen atmosphere at 0° C and allowed to stir overnight at room temperature. The reaction mixture was washed with 1N HCl (1 x 50 mL), 1N NaOH (1 x 50 mL), H_2O (3 x 50 mL) and brine (3 x 50 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent afforded a yellow oil (2.81 g, 8.3 mmol): R*f* = 0.47 (5% MeOH/$CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.7-2.0 (m, 3H), 2.1-2.2 (m, 1H), 3.3-3.5 (m, 2H), 3.7-3.9 (m, 2H), 3.9-4.0 (2 x s, 6H), 4.0-4.1 (s, 3H), 4.2-4.3 (m, 1H), 6.7 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.3, 156.5, 147.9, 143.5, 128.8, 104.8, 65.8, 62.6, 61.4, 61.2, 56.6, 50.2, 28.4, 28.1, 24.5, 14.2.

N-(2-Amino-3,4,5-trimethoxybenzoyl)pyrrolidine-2-methanol (117)

Hydrazine hydrate (1.33 mL, 41.5 mmol) was added dropwise to a solution of **116** (2.83 g, 8.3 mmol) in methanol (142 mL) gently refluxing over Raney nickel (500 mg, slurry). The resulting vigorous evolution of hydrogen gas subsided after approximately 10 minutes and the reaction was deemed to be complete by TLC after 2 h. The reaction mixture was filtered through celite and the solvent evaporated. Distilled water (100 mL) was added to

the residue, and the aqueous mixture was extracted with EtOAc (3 x 100 mL) and the combined organic phase washed with H_2O (3 x 100 mL) and brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the product (2.18 g, 6.5 mmol) as a brown oil: ^1H NMR (270 MHz, $CDCl_3$) δ 1.6-2.0 (m, 3H), 2.1-2.2 (m, 1H), 3.4-3.7 (m, 4H), 3.8 (s, 3H), 3.8-3.9 (2 x s, 6H), 4.4 (br s, 1H), 4.7-4.3 (br s, 1H), 6.6 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.7, 144.5, 141.6, 134.6, 107.1, 66.9, 61.0, 60.9, 60.5, 56.8, 50.9, 28.6, 24.9, 21.1, 14.2.

N-2-(Trichloroethoxycarbonylamino)-3,4,5-trimethoxybenzoyl)pyrrolidine-2-methanol (118)

A solution of 2,2,2-trichloroethylchloroformate (1.37 g, 6.5 mmol) in distilled dichloromethane (40 mL) was added dropwise over 0.5 h to a solution of anhydrous pyridine (0.93 g, 11.8 mmol) and the substrate, **117** (1.82 g, 5.9 mmol) in distilled dichloromethane (60 mL) at 0° C. After 1.5 h. the reaction mixture was diluted with anhydrous DCM (100 mL) and washed with 1N HCl (2 x 100 mL), H_2O (100 mL), brine (100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a brown oil which was purified by flash column chromatography eluting with 1% MeOH/ 99% $CHCl_3$ to afford the product as a yellow oil (1.83 g, 3.8 mmol): ^1H NMR (270 MHz, $CDCl_3$) δ 1.6-1.9 (m, 3H), 2.1-2.2 (m, 1H), 3.3-3.6 (m, 2H), 3.6-3.85 (m, 2H), 3.8-3.9 (m, 9H), 4.2-4.3 (m, 1H), 4.7-4.8 (br s, 1H), 4.8 (s, 2H), 6.6 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 169.9, 153.2, 151.9, 143.1, 128.5, 120.1, 105.2, 95.3, 74.6, 66.3, 61.2, 61.2, 61.0, 56.3, 50.6, 28.7, 24.6.

(11S,11aS)7,8,9-trimethoxy-11-hydroxy-10-N-(2',2',2'-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-c][1,4] benzodiazepin-5-one (119)

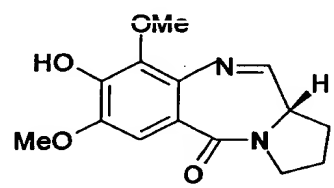
Anhydrous DMSO (3.15 mL, 44.3 mmol) in dry DCM (8.2 mL) was added dropwise over 20 mins to a stirred solution of oxalyl chloride (2.79 g, 11.0 mL of a 2N solution in DCM; 22.0 mmol) in dry DCM (20.6 mL) under an inert atmosphere at -45° C (varied between -38° and -48°C). After stirring for 15 mins, the substrate (7.59g; 15.6 mmol) in dry DCM (17 mL) was added dropwise over 45 mins to the reaction mixture, which was then stirred for a further 45 mins at -45°C after the final addition of the substrate. Dry TEA (4.84 g, 48.0 mmol, 4 eq) was added dropwise to the mixture over 0.5 h and stirred for a further 15 mins. The reaction mixture was allowed to warm to room temperature and the reaction mixture diluted with H_2O (80 mL). The organic phase was separated, washed with brine (2 x 100 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford the product as an off-white solid (4.39 g, 9.1 mmol): ^1H NMR (270 MHz, $CDCl_3$) δ 1.95-2.2 (m, 4H), 3.4-3.8 (m, 2H), 3.8-3.9 (m, 9H), 4.05 (d, 1H), 4.5-4.8 (dd, 2H), 5.6-5.7 (q, 1H), 7.1 (s, 1H); ^{13}C NMR ($CDCl_3$) rotamers δ 166.7, 166.5, 155.2, 153.5, 153.3, 150.0, 144.5, 129.5, 129.0, 121.7, 106.4, 106.2, 94.6, 86.1, 85.9, 75.7 75.2, 61.5, 61.3, 60.9, 60.1 59.8, 56.2, 56.1, 46.5, 46.3, 28.7, 28.6, 23.0.

7,8,9-Trimethoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (120, DRH-69)

10% Cd/Pb couple (1.25 g, 10 mmol Cd) was added to a rapidly stirring solution of the Troc-carbamate, 119 (1.00 g, 2.1 mmol)

in a mixture of THF (13 mL) and 1N NH_4OAc (8 mL). Upon addition, the reaction mixture went cloudy. After 40 minutes, TLC showed the reaction to be complete and the reaction mixture was diluted with EtOAc (200 mL). The solution was dried over anhydrous $MgSO_4$ and the solids were filtered and rinsed with EtOAc (50 mL). Evaporation of the solvent yielded the product as a yellow glass (0.581 g, 2.0 mmol). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.73 (d, 1H, J = 4.57 Hz), 7.08 (s, 1H), 4.0-3.4 (m, 12H), 2.4-1.8 (m, 4H)

<u>**Example 3(g): 8-Hydroxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (130, DRH-168)(see Figure 17)**</u>



Methyl 4-hydroxy-3,5-dimethoxybenzoate (121)

Concentrated sulphuric acid (3 mL), was added dropwise to a solution of 81 (20.24 g, 102.1 mmol) in refluxing methanol (70 mL). The reaction mixture was heated at reflux for a further 5 h and then cooled to room temperature and concentrated to a third of its original volume. The concentrate was poured onto crushed ice (c. 150 mL)and alowed to stand for 30 minutes. The aqueous mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic phase washed with distilled water (3 × 100 mL), brine (3 × 100 mL) and dried over anhydrous $MgSO_4$. Removal of ecxess solvent under reduced pressure afforded the product as a yellow solid, 121 (18.39 g, 86.7 mmol; ^{1}H NMR (270 MHz, $CDCl_3$) δ

3.9 (s, 3H), 3.95 (s, 3H), 3.975 (s, 3H), 6.1 (s, 1H), 7.3 (s, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.9, 146.6, 139.2, 121.0, 106.6, 56.4, 52.1.

Methyl 4-Benzyloxy-3,5-dimethoxybenzoate (122)

Benzyl chloride (11.04 g, 86.9 mmol) was added to a stirred solution of 121 (19.22 g, 90.8 mmol) over K_2CO_3 (6.59 g, 47.7 mmol) in anhydrous MeOH (175 mL) and the mixture was heated at reflux for 12 h. Excess solvent was removed under reduced pressure and the residue was extracted with benzene (3 x 100 mL). The organic layer was washed with H_2O (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded an orange oil which crystallised on standing. The solid was redissolved in EtOAc, and briefly washed with 1N NaOH (100 mL), H_2O (100 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation of excess solvent yielded the product as a yellow solid 122 (19.20 g, 63.6 mmol); ^1H NMR (270 MHz, $CDCl_3$) δ 3.8 (s, 3H), 3.85 (s, 3H), 3.9 (s, 3H), 5.1 (s, 2H), 7.3-7.5 (m, 7H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.7, 153.2, 140.8, 137.3, 128.7, 128.6, 128.4, 128.4, 128.2, 128.0, 127.7, 125.3, 106.7, 74.9, 56.1, 52.2.

Methyl 2-nitro-4-benzyloxy-3,5-dimethoxybenzoate (123)

Finely ground copper nitrate ($Cu(NO_3)_2$, 14.79 g, 78.7 mmol) was added portionwise to a vigorously stirred solution of the substrate (19.00 g, 62.9 mmol) in acetic anhydride (120 mL) whilst keeping the reaction temperature below 40° C. The

reaction mixture was stirred for 1 h and then poured over ice (800 mL). The aqueous mixture was left to stir for 1 h and the product collected by filtration to afford a yellow solid (18.7 g); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.19 (s, 2H), 7.3-7.5 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 163.2, 154.3, 146.0, 145.2, 136.2, 128.7, 128.5, 128.4, 128.3, 117.8, 108.52, 75.5, 62.7, 56.5, 53.0.

2-Nitro-4-benzyloxy-3,5-dimethoxybenzoic acid (124)

Potassium hydroxide (10.84 g, 193.6 mmol) was added to a stirred solution of the substrate (18.7 g, 53.9 mmol) in anhydrous methanol (220 mL) and the reaction mixture heated at reflux for 2 h. The reaction mixture was allowed to cool and acidified to pH2 with 1N HCl and extracted with chloroform (3 x 100 mL). The combined organic layers were washed with water (3 x 200 mL), brine (3 x 200 mL) and dried over $MgSO_4$. Evaporation of excess solvent by rotary evaporation under reduced pressure afforded the product as a yellow solid (17.01 g, 51.1 mmol, 95%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.9 (br s, 3H), 3.9 (br s, 3H), 5.1 (br s, 2H), 7.2-7.5 (m, 6H).

N-(4-Benzyloxy-3,5-dimethoxy-2-nitrobenzoyl)pyrrolidine-2-methanol (125)

A catalytic amount of DMF (5 drops) was added to a stirred solution of **124** (10g, 30.0 mmol) and oxalyl chloride (4.65 g, 36.0 mmol) in dry CH_3CN (115 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight and the

resulting acid chloride used directly in the next part of the procedure. 4-benzyloxy-3,5-dimethoxy-2-nitro-benzoyl chloride in anhydrous CH_3CN (115 mL) was added dropwise over 0.5 h to a stirring solution of pyrrolidine methanol (3.34 g, 33.03 mmol, 1.1 eq) and TEA (7.58 g, 75.1 mmol, 2.5 eq) in anhydrous DCM (100 mL) at 0° C under a nitrogen atmosphere and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was washed with 1N HCl (2 x 100 mL), and the organic layer was washed with distilled H_2O (2 x 100 mL), brine (2 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a brown glass (8.71 g, 20.9 mmol, 70%); ^1H NMR (270 MHz, $CDCl_3$) δ 1.7-2.2 (m, 4H), 3.3-3.5 (m, 2H), 3.7-3.9 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.2-4.3 (m, 1H), 5.1 (s, 2H), 6.85 (s, 1H), 7.3-7.5 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.3, 156.8, 148.2, 142.3, 136.4, 136.0, 129.0, 128.5, 128.4, 104.8, 75.6, 65.7, 62.8, 61.4, 56.6, 50.2, 28.3, 24.5.

N-(2-Amino-4-Benzyloxy-3,5-dimethoxybenzoyl)pyrrolidine-2-methanol (126)

Hydrazine hydrate (2.31 g, 72.2 mmol) was added dropwise to a solution of **125** (6.01 g, 14.4 mmol) in methanol (60 mL) gently refluxing over Raney nickel (1.1g, slurry). The resulting vigorous evolution of hydrogen gas subsided after approximately 10 minutes and the reaction was deemed to be complete by TLC after 2 h. The reaction mixture was filtered through celite and the solvent evaporated. Distilled water (100 mL) was added to the residue, and the aqueous mixture was extracted with EtOAc (3 x 100 mL) and the combined organic phase washed with H_2O (3 x 100

mL) and brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the produc as a brown oil (3.97 g, 10.3mmol, 73%): ^1H NMR (270 MHz, $CDCl_3$) δ 1.6-2.2 (m, 4H), 3.5-3.8 (m, 4H), 3.8 (s, 3H), 3.9 (s, 3H), 4.4 (br s, 1H), 5.1 (s, 2H), 6.6 (s, 1H), 7.3-7.6 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.5, 144.9, 143.5, 141.9, 137.5, 134.6, 128.6, 128.5, 128.3, 128.2, 128.0, 115.1, 107.3, 75.1, 66.9, 61.0, 60.6, 60.4, 56.9, 50.9, 28.5, 24.9, 21.1, 14.2.

N-(4-Benzyloxy-3,5-dimethoxy-2-[(2'-trimethylsilylethoxy)carbonylamino[benzoyl)pyrrolidine-2-methanol (127)

A solution of anhydrous pyridine (0.21 g, 2.6 mmol) in anhydrous DCM (10 mL) was added dropwise over 15 minutes to a stirred solution of 2-(trimethylsilyl)ethanol (0.92 g, 7.8 mmol) and triphosgene (0.77 g, 2.6 mmol) in anhydrous DCM (30 mL). The reaction mixture was allowed to stir overnight and the resulting solution of 2-(trimethylsilyl)ethyl chloroformate added dropwise over 0.5 h to the amine **126** (1.98 g, 5.1 mmol) and anhydrous pyridine (1.22 g, 15.4 mmol) in distilled dichloromethane (70 mL) at 0°C. The reaction mixture was allowed to stir overnight at room temperature, diluted with anhydrous DCM (100 mL), washed with 1N HCl (3 x 100 mL), H_2O (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent yielded the product as a colourless glass (1.43 g, 2.7 mmol, 53%); ^1H NMR (270 MHz, $CDCl_3$) δ -0.05 (s, 9H), 0.94-0.99 (m, 2H), 1.66-2.12 (m, 4H), 3.32-3.54 (m, 2H), 3.74-3.88 (m, 8H), 4.05-4.22 (m, 3H), 4.69 (br s, 1H), 4.97 (s, 2H), 6.57 (s,

1H), 6.64 (br s, 1H), 7.23-7.43 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 170.1, 155.1, 151.4, 148.1, 142.0, 137.1, 128.4, 128.3, 128.1, 121.2, 105.6, 75.3, 66.1, 64.0, 61.3, 61.0, 56.3, 50.6, 28.7, 24.7, 17.6, -1.5.

(11S,11aS)-8-benzyloxy-7,9-dimethoxy-11-hydroxy-10-N-(2'-trimethylsilylethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one. (128)

Anhydrous DMSO (0.57 g, 7.2 mmol) in dry DCM (5 mL) was added dropwise over 30 minutes to a stirred solution of oxalyl chloride (0.46 g, 3.6 mmol) in dry DCM (5 mL) under a nitrogen atmosphere at -45°C. After stirring for 15 minutes, the substrate (1.35 g, 2.6 mmol) in dry DCM (15 mL) was added dropwise over 45 minutes to the reaction mixture, which was then stirred for a further 45 minutes at -45°C. TEA (1.0 g, 10.2 mmol) was added dropwise to the mixture over 0.5 h and stirred for a further 15 mins. The reaction mixture was left to warm to room temperature and diluted with H_2O (100 mL) and the phases separated. The organic phase was washed with 1N HCl (3 x 50 mL), water (3 x 50 mL), brine (3 x 50 mL) and dried over $MgSO_4$. Filtration and evaporation of excess solvent afforded the product as an off-white glass (1.24 g, 2.3 mmol, 92%); ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.05 (s, 9H), 0.88-0.95 (m, 2H), 2.06-2.23 (m, 4H), 3.46-3.64 (m, 2H), 3.75-4.02 (m, 7H), 4.11-4.27 (m, 2H), 5.13 (s, 2H), 5.65 (d, 1H, J = 9.71 Hz), 7.11 (s, 1H), 7.34-7.54 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.8, 157.2, 153.1, 150.5, 143.4, 137.1, 129.2, 128.4, 128.3, 128.3, 128.1, 123.0, 106.2, 85.7, 75.0, 64.7, 61.7, 59.8, 56.1, 46.4, 28.6, 23.0, 17.5, -1.5, -1.6.

(11S,11aS)-8,11-dihydroxy-7,9-dimethoxy-10-N-(2'-trimethylsilylethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one(129)

10% Pd/C catalyst (0.22 g) was added to a solution of the substrate **128** (0.95g, 2.1 mmol) in absolute EtOH (200 mL). The reaction mixture was hydrogenated under pressure using a Parr hydrogenator at 55 psi H_2 for 18 h. The reaction mixture was filtered through celite, and the celite washed with hot EtOH, taking care not to allow the filtration pad to dry out. Removal of excess solvent afforded the product as a colourless glass (0.84 g, 1.9 mmol, 92%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.91-0.97 (m, 2H), 2.07-2.20 (m, 4H), 3.52—3.75 (m, 2H), 3.98-4.26 (m, 9H), 5.65 (d, 1H, J = 9.71 Hz), 6.26 (br s, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 167.0, 157.3, 146.8, 143.4, 141.3, 124.9, 123.5, 105.5, 105.2, 85.8, 64.8, 64.6, 64.5, 61.2, 60.0, 56.4, 46.4, 28.9, 28.7, 23.1, 23.0, 17.3, -1.3, -1.5, -1.7.

7,9-dimethoxy-8-Hydroxy-1,2,3,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-2-one (130)

A solution of TBAF in THF (4.3 mL of a 1N solution, 4.3 mmol) was added to a rapidly stirred solution of **129** (0.37 g, 0.9 mmol) in THF (10 mL) and the reaction mixture heated to 35° C for 2 h. The reaction mixture was diluted with EtOAc (50 mL), dried over anhydrous $MgSO_4$, filtered and removal of excess solvent by rotary evaporation under reduced pressure afforded the product as a brown oil (0.18 g, 0.7 mmol, 78%). H^1 NMR ($CDCl_3$) mixture of C11/C11'R/S carbinolamine methyl ethers δ 7.08 (s, 1H), 4.43 (d, 1H, J = 8.79 Hz), 4.05-3.23 (m, 12H), 2.3-1.48 (m, 4H).

Examples 3(h) to (j): Synthesis of 7-Phenyl PBDs (See Figure 18)

Synthesis of the 7-Iodo-N10-Troc-PBD Intermediate (134, AG/91)

5-Iodo-2-(2',2',2'-trichloroethoxycarbonylamino)benzoic acid (132)

A solution of Troc-Cl (2.88 mL, 20.9 mmol) in dry dichloromethane (20 mL) was added drop wise to a solution of 5-iodoanthranilic acid 131 (5 g, 19 mmol) and pyridine (3.1 mL, 38 mmol) in dry dichloromethane (30 mL) at 0° C. The solution was stirred for 5 hours at room temperature and then washed with 1N HCl (2 x 25 mL), water (1 x 25 mL) and brine (1 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated, residue was recrystallized from ethyl acetate to afford the title compound as a yellow solid (6.2 g, 75%): m.p. 248 C (ethyl acetate). ^1H NMR ($CDCl_3$, DMSO-d_6) δ 4.83 (s, 2H); 7.78-7.82 (dd, J = 9.2, J = 2.2 Hz, 1H); 8.18 (d, J = 9 Hz, 1H); 8.38 (d, J = 2.2 Hz, 1H); 9.0-10.5 (bs, 1H); 11.04 (s, 1H). ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 74.4, 84.6, 95.2, 117.7, 120.7, 140, 140.8, 142.8, 151.5, 169. MS: m/e (relative intensity) 437 (M-1, 60), 289 (55), 272 (37), 245 (100), 218 (27). HRMS Calculated for $C_{10}H_7Cl_3INO_4$: 436.8485. Found: 436.8485.

N-(5-Iodo-(2',2',2'-trichloroethoxycarbonylamino)benzoyl) pyrrolidine-2-methanol (133)

Oxalyl chloride (0.88 mL, 10 mmol) was added to a suspension of 132 (4 g, 9.1 mmol) in dry dichloromethane (50 mL), followed by 3-4 drops of DMF as catalyst. The solution was stirred at room

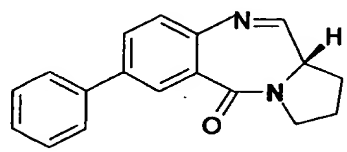
temperature for 12 hours, and then used directly in the next step. The newly formed acid chloride was added drop wise, over 1 hour, to a solution of 2*S*-(+)-pyrrolidinemethanol (1.01 g, 10 mmol) and triethylamine (3.16 mL, 22.7 mmol) in dry dichloromethane (50 mL) at -20°C. The reaction mixture was allowed to stir for a further hour at -20°C and was then washed with dilute HCl (1N, 2 x 50 mL), water (50 mL) and brine (50 mL), dried over $MgSO_4$ and evaporated. The crude product was subjected to flash column chromatography to afford the title compound as a pale yellow oil (3.8 g, 81%): ^1H NMR ($CDCl_3$, DMSO-d_6) δ 1.77-2.28 (m, 4H); 3.48 (bs, 2H); 3.7 (dd, *J* = 11.4, *J* = 6.2, 1H); 3.94 (d, *J* = 11.4 Hz, 1H); 4.40 (bs, 1H); 4.75 (d, *J* = 12 Hz, 1H); 4.84 (d, *J* = 12 Hz, 1H); 7.66 - 7.72 (m, 2H); 7.85 (d, *J* = 8.6 Hz, 1H); 8.91 (bs, 1H). ^{13}C NMR ($CDCl_3$, DMSO-d_6) δ 25.0, 28.1, 51.2, 60.7, 65.3, 74.5, 86.1, 95.1, 123.0, 128.0, 135.6, 136.1, 139.8, 151.8, 168.4. IR (Nujol): cm^{-1} 3415, 3215, 1745, 1605, 1527, 1445, 1377, 1221, 1101, 1056, 822, 733. MS: m/e (relative intensity) 522 ($M^{+\cdot}$, 3), 521 ($M^{+\cdot}$, 1), 520 ($M^{+\cdot}$, 3), 491 (3), 490 (1), 489 (3), 372 (7), 341 (28), 272 (80), 245 (14), 216 (14), 83 (15), 70 (100). HRMS Calculated for $C_{15}H_16Cl_3IN_2O_4$: 521.9193. Found: 521.9125. $[a]^{25}_D$= +123.4° (*c* = 2.8, CHCl3).

7-Iodo-10-N-(2′,2′,2′-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzo- diazepin-5-one (134)

A solution of DMSO (1.79 mL, 25.67 mmol) in dry dichloromethane (35 mL) was slowly added (30 minutes) to a solution of oxalyl chloride (12.8 mmol) in dry dichloromethane (41.4 mL) at - 45° C. The mixture was allowed to stir for 25 minutes and then treated

with a solution of 133 (4.78 g, 9.2 mmol), in dry dichloromethane (80 mL), keeping temperature below -40° C. After further 60 minutes at -45° C, a solution of triethylamine (5.1 mL) in of dichloromethane (25 mL) was added, and the reaction mixture allowed to warm to room temperature. The organic phase was washed with water (180 mL), dilute HCl (1N, 2 x 100 mL) and brine (200 mL). Removal of excess solvent afforded the crude product which was purified by flash chromatography (ethyl acetate/petroleum ether 70/30) to give of a pale yellow oil (3.6 g, 76%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.02-2.15 (m, 4H); 3.37-3.60 (m, 2H); 3.70-3.77 (m, 1H); 4.19 (bs, 1H); 4.28 (d, J = 12 Hz, 1H); 5.17 (d, J = 12 Hz, 1H); 5.66 (d, J = 9.7 Hz, 1H); 7.10 (d, J = 8.3 Hz, 1H); 7.79 (dd, J = 8.3, J = 2.2 Hz, 1H); 8.10 (d, J = 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 23.0, 28.8, 46.5, 59.6, 75.1, 86.0, 93.2, 94.8, 132.0, 133.6, 135.0, 137.9, 140.1, 154.1, 165.2. IR (Nujol): cm^{-1} 3500-3000, 1716, 1619, 1458, 1376, 1312, 1075, 720. MS: m/e (relative intensity) 520 ($M^{+\cdot}$, 62), 519 (22), 518 (62), 491 (15), 371 (19), 342 (39), 272 (84), 216 (31), 119 (27), 70 (100). HRMS Calculated for $C_{15}H_{14}Cl_3IN_2O_4$: 519.9036. Found: 519.9037. $[a]^{25}_{D}$ = +137.4° (c = 1.15, CHCl3).

<u>Example 3(h): Synthesis of the 7-Phenyl-PBD (136, AG/129)</u>



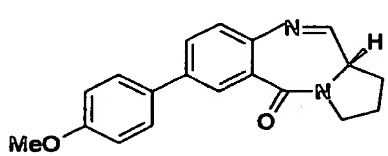
7-Phenyl-10-N-(2',2',2'-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5-H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one (135)

A suspension of **134** (0.5 g, 1.0 mmol), benzeneboronic acid (0.15 g, 1.22 mmol), $Pd(PPh_3)_4$ and anhydrous Na_2CO_3 (0.16 g, 1.48 mmol) in distilled benzene (20 mL), water (2 ml) and ethanol (2 mL) was heated at reflux overnight. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 20 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield a crude yellow oil. Purification by flash chromatography (ethyl acetate/petroleum ether 30/70 to 70/30) furnished the title compound (0.43 g, 95%): ^1H NMR (270 MHz, $CDCl_3$) δ 1.98-2.09 (m, 2H); 2.12-2.15 (m, 2H); 3.51-3.62 (m, 2H); 3.7-3.79 (m, 1H); 4.28 (d, J = 12.1 Hz, 1H); 4.73 (d, J = 4.4 Hz, 1H); 5.18 (d, J = 12.1 Hz, 1H); 5.66-5.73 (dd, J = 4.8, J = 9.8 Hz, 1H); 7.33-7.48 (m, 4H); 7.61-7.70 (m, 3H); 8.02 (d, J = 2.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.9, 28.7, 46.4; 59.8; 75.0; 77.3; 86.0; 94.9; 127.0; 127.3; 128.0; 128.9; 129.6; 130.8; 132.9; 133.5; 139.2; 141.1; 154.4; 166.9. MS: m/e (relative intensity) 468 ($M^{+\cdot}$, 10), 292 (25), 222 (100), 195 (10), 166 (35), 140 (10), 70 (70). HRMS Calculated for $C_{21}H_{19}Cl_3N_2O_4$: 468.0411. Found: 468.0410. $[a]^{25}_{D}$ = + 103.8° (c = 0.42, $CHCl_3$).

(11aS)-7-Phenyl-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one (136, AG/129)

Cd/Pb (0.47 g) couple was added portion wise to a vigorously stirred solution of 135 (0.33 g, 0.7 mmol) in THF (5 mL) and of aq. ammonium acetate (1M, 5mL). The suspension was allowed to stir at room temperature for 2 hours, then poured into ethyl acetate (200 mL), dried with $MgSO_4$ and filtered. The filtrate was evaporated and the residue purified by flash column chromatography (ethyl acetate) to afford the title compound as colourless oil (0.19 g, 98%): ^1H NMR (270 MHz, $CDCl_3$) δ 2.0-2.12 (m, 2H); 2.29-2.37 (m, 2H); 3.53-3.63 (m, 1H); 3.76-3.92 (m, 2H); 7.36-7.79 (m, 8H); 8.28 (d, J = 2.2 Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.4; 29.8; 46.9; 53.8; 126.9; 127.3; 127.7; 128.0; 128.2; 128.8; 128.9; 129.1; 130.1; 130.5; 139.5; 145.0; 164.5; 165.1. IR (Nujol): cm^{-1} 3000-2800, 1620, 1455, 1377, 1239, 1239, 1014, 990, 761,728, 697. HRMS Calculated for $C_{18}H_16N_2O$: 276.1261. Found: 276.1262. $[a]^{25}_D = + 131.4°$ (c = 0.19, CHCl3).

__Example 3(i): Synthesis of the 7-(4'-Methoxyphenyl)-PBD (138, AG/135)__



(11S,11aS)-7-(4'-Methoxy)phenyl-11-hydroxy-10-N-(2'',2'',2''-trichloroethoxycarbonyl)-1,2,3,10,11a-hexahydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-5-one (137)

134 (0.5 g, 1.0 mmol), 4-methoxybenzeneboronic acid (0.19 g, 1.2

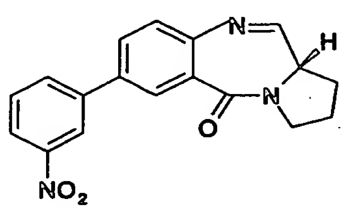
mmol), $Pd(PPh_3)_4$ (15 mg) and anhydrous Na_2CO_3 (0.16 g, 1.48 mmol) were heated at reflux, over night, in a mixture of distilled benzene (20 mL), ethanol (2 mL) and water (2 mL). The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 20 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield a crude yellow oil. Purification by flash chromatography (ethyl acetate/petroleum ether 50/50) afforded the pure compound (0.34 g, 71%): ^1H NMR ($CDCl_3$) δ 1.96-2.16 (m, 4H); 3.54-3.63 (m, 2H); 3.71-3.79 (m, 1H); 3.85 (s, 3H); 4.18 (d, J = 4.8 Hz, 1H); 4.29 (d, J = 12.1 Hz, 1H); 5.20 (d, J = 12.1 Hz, 1H); 5.66-5.72 (dd, J = 4.5, J = 9.8 Hz, 1H); 6.97 (d, J = 8.8 Hz, 2H); 7.37 (d, J = 8.2 Hz, 1H); 7.57 (d, J = 8.8 Hz, 2H); 7.64 (dd, J = 2.4, J = 8.2 Hz, 1H); 7.97 (d, J = 2 Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.0; 28.7; 46.4; 55.4; 59.6; 75.1; 86.1; 94.9; 114.3; 126.8; 129.1; 130.6; 131.7; 132.0; 132.2; 132.3; 133.5; 140.7; 154.5; 159.6; 166.9. IR (Nujol): cm^{-1} 3000-2800, 1740, 1620, 1462, 1378, 1247, 1082, 816, 721. MS: m/e (relative intensity) 498 ($M^{+\cdot}$, 15), 350 (20), 321 (15), 252 (100), 196 (22), 182 (5), 126 (7), 70 (28). HRMS Calculated for $C_{22}H_{21}Cl_3N_2O_5$: 498.0515. Found: 498.0513. $[a]^{25}_D = +149.4^\circ$ (0.25, $CHCl_3$)

(11aS)-7-(4′-Methoxyphenyl)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-5-one (138, AG/135)

Cd/Pb couple (0.51 g) was added portion wise to a, vigorously stirred, solution of 137 (0.34 g, 0.76 mmol) in THF(5 mL) and aq. ammonium acetate (1M, 5 mL). The suspension was allowed to stir at room temperature for 2 hours, then poured into ethyl

acetate (200 mL), dried over $MgSO_4$ and filtered. The organic solution was evaporated and the residue purified by flash column chromatography (ethyl acetate), to afford the title compound as colourless oil (0.1 g, 70%): ^1H NMR ($CDCl_3$, DMSO-d_6) δ 2.1 (m, 2H); 2.3-2.4 (m, 2H); 3.5-3.62 (m, 1H); 3.85 (m, 5H); 7.0 (d, J = 8.8 Hz, 2H); 7.36 (d, J = 8.3 Hz, 2H); 7.6 (d, J = 8.8 Hz, 2H); 7.72 (dd, J = 2.2, J = 8.2 Hz 1H); 7.8 (d, J = 4.4 Hz, 1H,); 8.2 (d, J = 2.2 Hz, 1H). ^{13}C NMR (270 MHz, $CDCl_3$, DMSO-d_6) δ 24.1; 29.5; 46.7; 53.6; 55.3; 77.3; 114.1; 114.3; 127.4; 127.6; 127.8; 128.0; 129.3; 131.9; 138.7; 144.3; 159.4; 164.2; 164.8. IR (Nujol): cm^{-1} 3000-2800, 1662, 1607, 1491, 1454, 1245, 1069, 823, 759. MS: m/e (relative intensity) 306 ($M^{+\cdot}$, 100), 277 (15), 237 (10), 182 (12), 153 (10), 132 (5), 70 (10). HRMS Calculated for $C_{19}H_18N_2O_2$: 306.1367. Found: 306.1365. $[a]^{25}_D$ = + 773.1° (c = 0.11, CH_3OH).

<u>Example 3(j): Synthesis of the 7-(3'-Nitrophenyl)-PBD (140, AG/150)</u>



(11S,11aS)-7-(3'-Nitro)phenyl-11-hydroxy-10-N-(2'',2'',2''-trichloroethoxycarbonyl)-1,2,3,10,11a-hexahydro-5H-pyrrolo[2,1-c]-[1,4]benzodiazepin-5-one (139)

134(0.5 g, 1.0 mmol), 3-nitrobenzeneboronic acid (0.2 g, 1.2 mmol), $Pd(PPh_3)_4$ (25 mg) and anhydrous Na_2CO_3 (0.16 g, 1.48 mmol)

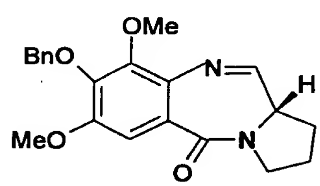
were heated at reflux, over night, in a mixture of distilled benzene (20 mL), ethanol (2 mL) and water (2 mL). The reaction mixture was diluted with ethyl acetate (20 ml) and washed with water (2 x 20 ml). The organic phase was dried over $MgSO_4$ and evaporated to yield a crude yellow oil. Purification by flash chromatography (ethyl acetate/petroleum ether 50/50) afforded the pure compound (0.45 g, 90%): ^1H NMR (270 MHz, $CDCl_3$) δ 2.0-2.2 (m, 4H); 3.6 (m, 2H); 3.76 (m, 1H); 4.31 (d, J = 12 Hz, 1H); 5.19 (d, J = 12 Hz, 1H); 5.76 (d, J = 10 Hz, 1H); 7.5-8.5 (m, 8H). ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 22.9, 28.7, 46.4, 59.7, 75.0, 86.0, 94.8, 121.7, 122.6, 127.5, 129.4, 129.9, 131.2, 132.0, 132.8, 133.9, 138.3, 140.7, 148.6, 154.1, 166.3. IR (Nujol): cm^{-1} 3000-2800, 1721, 1626, 1530, 1455, 1349, 1062, 821, 759. MS: m/e (relative intensity) 513 ($M^{+\cdot}$), 336 (55), 321 (100), 292 (15), 267 (54), 221 (16), 197 (18), 164 (15), 70 (22). HRMS Calculated for $C_{21}H_{18}Cl_3N_3O_6$: 515.0233. Found: 515.0235. $[a]^{25}_D = +129.6^\circ$ (c = 0.1, CH_3OH).

(11aS)-7-(3′-Nitrophenyl)-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (140, AG-150)

A solution of TBAF in THF (1M solution, 7.6 mL, 7.6 mmol) was added to a solution 139 (0.39 g, 0.8 mmol) in of THF (20 mL) and the reaction mixture allowed to stir for 2 hours at room temperature. The solution was diluted with ethyl acetate (50 mL) and washed with water (3 x 50 mL) to remove excess TBAF. The organic phase was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash column chromatography ($CHCl_3$), to afford the title compound as a colourless oil (0.15 g, 63%):

^1H NMR (270 MHz, $CDCl_3$) δ 1.8-2.2 (m, 3H); 3.5-4.0 (m, 3H); 7.3-8.5 (m, 7H). IR (Nujol): cm^{-1} 3000-2850, 1624, 1527, 1466, 1349, 1244, 757, 740. MS: m/e (relative intensity) 321 ($M^{+\cdot}$, 100), 292 (8), 265 (5), 224 (5), 197 (7), 151 (5), 70 (5). HRMS Calculated for $C_{18}H_{15}N_3O_3$: 321.1115. Found: 321.1113. $[a]^{25}_D$ = + 129.6° (*c* = 0.1, CH_3OH).

__Example 3(k): 8-Benzyloxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (143, DRH-105) (see Figure 19__



N-(4-Benzyloxy-3,5-dimethoxy-2-[trichloroethyloxycarbonylamino]benzoyl)pyrrolidine-2-methanol (141)

A solution of 2,2,2-trichloroethyl chloroformate (1.08 g, 4.8 mmol) in distilled dichloromethane (10 mL) was added dropwise over 0.5 h to a solution of anhydrous pyridine (0.80 g, 10.1 mmol) and **126** (Example 3(g))(1.95 g, 5.1 mmol) in distilled dichloromethane (20 mL) at 0° C. After 1 h the reaction mixture was diluted with anhydrous DCM (100 mL) and washed with 1N HCl (2 x 100 mL), H_2O (100 mL), brine (100 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded a brown oil which was purified by flash column chromatography (silica gel, EtOAc) to afford the product as a yellow glass (2.65 g, 4.7 mmol, 94%); ^1H

NMR (270 MHz, $CDCl_3$) δ 1.6-2.2 (m, 4H), 3.3-3.6 (m, 2H), 3.6-3.9 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 4.2-4.3 (m, 1H), 4.8 (s, 2H), 5.1 (s, 2H), 6.6 (s, 1H), 7.2 (br s, 1H), 7.3-7.5 (m, 5H); ^{13}C NMR (67.8 MHZ, $CDCl_3$) δ 171.5, 153.1, 142.0, 137.023, 128.3, 128.3, 128.2, 120.1, 105.3, 95.4, 75.3, 74.6, 66.5, 61.4, 61.3, 56.3, 50.7, 28.7, 24.6.

(11S,11aS)-8-benzyloxy-7,9-dimethoxy-11-hydroxy-10-N-(2',2',2'-trichloroethoxylcarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4] benzodiazepin-5-one (142)

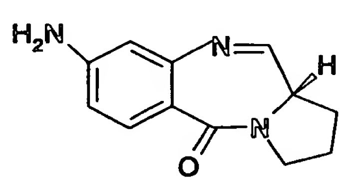
Anhydrous DMSO (0.97 g, 12.5 mmol) in dry DCM (10 mL) was added dropwise over 30 minutes to a stirred solution of oxalyl chloride (3.08 mL of a 2N solution in DCM, 6.2 mmol) in dry DCM (10mL) under a nitrogen atmosphere at -45° C. After stirring for 15 mins, the substrate (2.46 g, 4.38 mmol) in dry DCM (25 mL) was added dropwise over 45 minutes to the reaction mixture, which was then stirred for a further 45 minutes at -45° C. TEA (1.77 g; 17.5 mmol) was added dropwise to the mixture over 0.5 h and stirred for a further 15 minutes. The reaction mixture was left to warm to room temperature, diluted with H_2O (100 mL)and the phases allowed to separate. The organic phase was washed with 1N HCl (2 x 50 mL), water (2 x 50 mL), brine (2 x 50 mL) and dried over $MgSO_4$. The solvent was evaporated to afford the product as an off-white glass (3.92 g, 11.7 mmol; 97 %); ^1H NMR (270 MHz, $CDCl_3$) δ 2.01-2.17 (m, 4H), 3.44-3.77 (m, 2H), 3.87-3.90 (m, 1H), 3.88 (s, 3H), 3.91 (s, 3H), 4.68 (dd, 2H), 5.01 (s, 2H), 5.62 (d, 1H), 7.08 (s, 1H), 7.27-7.48 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.7, 155.2, 153.6, 150.5, 143.6, 137.1, 129.8, 129.3, 128.4,

128.3, 128.2, 128.1, 121.8, 106.5, 106.3, 94.7, 86.2, 85.9, 75.6, 75.4, 75.2, 75.0, 61.8, 61.5, 60.2, 59.870, 56.1, 56.0, 46.5, 46.3, 45.8, 28.7, 28.6, 23.0.

8-Benzyloxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-c][1,4]benzodiazepin-5-one (143)

10% Cd/Pb couple (1.2 g; 10 mmol Cd) was added to a rapidly stirring solution of **142** (1.08 g; 1.9 mmol) in a mixture of THF (15 mL) and 1N NH_4OAc (15 mL). After 3.5 h, TLC revealed that reaction was still incomplete and more 10% Cd/Pb couple (500 mg) was added. After a further 1 h the reaction mixture was diluted with EtOAc (150 mL). The solution was dried over anhydrous $MgSO_4$ and the solids were filtered and rinsed with EtOAc (50 mL). Removal of excess solvent yielded the product as a yellow glass (0.48 g, 1.3 mmol, 68%). H^1 NMR (270 MHz, $CDCl_3$) δ 7.73 (d, 1H, J = 4.4 Hz), 7.36 (s, 2H), 7.31 (s, 2H), 7.11 (s, 1H), 7.08 (s, 1H), 5.12 (br s, 2H), 3.98-3.42 (m, 9H), 2.38-2.29 (m, 2H), 2.23-1.83 (m, 2H).

__Example 3(1): Synthesis of the C8-NH2 PBD (157, AG/149)(see Figure 20)__



4-Nitro-2-(2',2',2'-trichloroethoxycarbonylamino)benzoic acid (145)

A solution of 2,2,2-trichloroethylchloroformate (Troc-Cl) (1.66

mL, 12.1 mmol) in dry dichloromethane (25 mL) was added drop wise to a solution of 4-nitroanthranilic acid **144** (2 g, 11 mmol) and pyridine (1.78 mL, 22 mmol) in dichloromethane (25 ml) at 0° C. The solution was allowed to stir at 25° C for 5 hours. The reaction mixture was washed with dilute HCl (1N, 2 x 50 mL), water (1 x 50 mL), brine (1 x 2 5 mL) and dried over $MgSO_4$. Removal of excess solvent by rotary evaporation under reduced pressure afforded the crude product which was used in the subsequent reaction without further purification.

N-[4-nitro-(2′,2′,2′-trichloroethoxycarbonylamino) benzoyl] pyrrolidine-2-methanol (146)

Oxalyl chloride (1 mL, 12.1 mmol) and a catalytic amount of dry DMF were added to a suspension of the crude product from the previous reaction in of dry dichloromethane (50 mL) and the reaction mixture was allowed to stir at room temperature for 12 hours. The newly formed acid chloride was added drop wise, over 1 hour, to a solution of 2*S*-(+)-pyrrolidinemethanol (1.22 g, 12.1 mmol) and triethylamine (3.8 mL, 27.5 mmol) in dichloromethane (50 mL) at -20° C (CCl_4-dry ice). The reaction mixture was stirred for a further hour at -20° C and was then allowed to warm to room temperature. The reaction mixture was washed with dilute HCl (1N, 2 x 50 mL), water (50 mL) and brine (50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether 50/50), removal of excess eluent afforded of a yellow oil (1.34 g, 30%, over two steps): ^1H NMR (270 MHz, $CDCl_3$) δ 1.7 - 2.3 (m, 4H); 3.45 (m, 2H); 3.71 (dd, J = 5.5, J = 11, 1H); 4.06 (m, 2H); 4.43

(bs, 1H); 4.85 (d, J = 13, 1H); 4.89 (d, J = 13 Hz, 1H); 7.56 (d, J = 8.4 Hz, 1H); 7.96 (dd, J = 2.2, J = 8.4 Hz, 1H); 8.94 (d, J = 2.2 Hz, 1H); 9.2 (bs, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.9; 27.9; 50.8; 60.5; 64.3; 74.6; 94.9; 115.9; 117.9; 128.6; 130.5; 136.9; 149.0; 151.8; 167.7. MS: m/e (relative intensity) 441 ([M+1], 1), 291 (10), 260 (12), 191 (30), 164 (15), 154 (8), 113 (20), 77 (20), 70 (100). HRMS Calculated for $C_{15}H_16C_13N_3O_6$: 439.0104. Found: 439.0105. $[a]^{25}_D$ = - 110.6° (c = 0.13, CHCl3).

N-[4-amino(2',2',2'-trichloroethoxycarbonylamino)benzoyl] pyrrolidine-2-methanol (147)

A solution of **146** (1 g, 2.3 mmol) and $SnCl_2$ $2H_2O$ (2.56 g, 11.4 mmol) in methanol (20 mL) was heated at reflux for 6 hours (the reaction was monitored by TLC (3% methanol, ethyl acetate). The reaction mixture was reduced to 1/3 of it's original volume and the pH adjusted to 8-9 with satd. aqueous $NaHCO_3$. Ethyl acetate (100 mL) was added and the mixture was vigorously stirred for 12 hours, then filtered through Celite to remove tin salts. The organic phase was dried over $MgSO_4$ and evaporated to afford the product as a yellow oil (0.94 g, 97%) which was used in the next reaction without further purification: ^1H NMR (270 MHz, $CDCl_3$) δ 1.6 - 1.8 (m, 2H); 1.9 (m, 1H); 2.17 (m, 1H); 3.48 - 3.58 (m, 1H); 3.62 - 3.72 (m, 2H); 3.84 (m, 1H); 4.44 (m, 1H); 4.77 (d, J = 12.1 Hz , 1H); 4.83 (d, J = 12.1 Hz, 1H); 6.32 (dd, J = 2.2, J = 8.43 Hz, 1H); 7.18 (d, J = 8.43 Hz, 1H); 7.52 (d, J = 2.2 Hz, 1H); 9.62 (bs, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.1; 25.2; 28.2; 51.9; 60.9; 66.5; 74.3; 95.3; 105.5; 108.3; 112.6; 130.1; 138.9; 149.7; 151.8; 171.5. IR (Nujol): cm^{-1} 3346, 3000-2800,

1738, 1620, 1463, 1196, 1046, 963, 820 760. MS: m/e (relative intensity) 409 ([M-1], 15), 309 (20), 179 (25), 161 (100), 134 (8), 113 (25), 77 (35), 70 (85). HRMS Calculated for $C_{15}H_{1}8Cl_{3}N_{3}O_{4}$: 409.0362. Found: 409.0363. $[a]^{25}{}_{D}$ = - 60.1° (c = 0.3, $CHCl_3$).

N-[4-(Fmoc)amino(2',2',2'-trichloroethoxycarbonylamino)benzoyl] pyrrolidine-2-methanol (148)

An aqueous solution of $NaHCO_3$ (0.6 g, 5.67 mmol, in 20 mL of H_2O) was added to a solution of **147** (0.94 g, 2.3 mmol) in THF (20 mL). The reaction mixture was cooled to 0° C and Fmoc-Cl (0.65 g, 2.5 mmol) was added in small portions. After addition the reaction mixture was allowed to stir for 2 hours at room temperature. (TLC: ethyl acetate /petroleum ether 50/50). The reaction mixture was acidified with dilute HCl (1N) and extracted with ethyl acetate (2 x 20 mL). The organic phase was dried ($MgSO_4$) and evaporated and the resulting yellow oil thus obtained was purified by flash chromatography to afford the product (1.03 g, 72%): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.68 (m, 2H); 1.84 (m, 1H); 2.11 (m, 1H); 3.48 (m, 2H); 3.71 (m, 1H); 3.87 (m, 1H); 4.19 (t, J = 6.8 Hz, 1H); 4.40 (m, 2H); 4.45 (d, J = 6.78 Hz, 2H); 4.73 (d, J = 12.1, 1H); 4.78 (d, J = 12.1 Hz, 1H); 7.2 - 7.8 (m, 11H); 8.04 (bs, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.1; 28.1; 46.8; 51.6; 60.8; 65.7; 67.1; 74.3; 95.2; 109.9; 112.3; 118.3; 120.0; 124.9; 127.1; 127.8; 129.3; 137.5; 140.9; 141.2; 143.6; 151.8; 153.2; 170.3. IR (Nujol): cm^{-1} 3301, 3000-2800, 1738, 1599, 1525, 1451, 1224, 1056, 985, 758, 740, 667. MS: m/e (relative intensity) 632 ($M^{+\cdot}$), 409 (15), 309 (20), 179 (25), 161 (100), 134 (8), 113

(25), 77 (35), 70 (85). $[a]^{25}_{D} = -70.3^{\circ}$ (c = 0.25, CHCl3).

(11S,11aS)-8-(Fmoc)amino-11-hydroxy-10-N-(2′,2′,2′-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (149)

A solution of DMSO (0.31 ml, 4.4 mmol) in of dry dichloromethane (10 mL) was slowly added (over 30 minutes) to a solution of oxalyl chloride (2.2 mmol) in dry dichloromethane (11.1 mL) at -45° C. The mixture was allowed to stir for 15 minutes followed by the addition of a solution of **148** (1 g, 1.58 mmol) in of dry dichloromethane (15 ml), keeping the temperature below -40° C. After further 60 minutes at -45° C, a solution of triethylamine (0.88 ml 6.32 mmol) in dichloromethane (6 mL) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was washed with water (50 mL), dilute HCl (1N, 50 mL) and brine (50 mL). Evaporation of solvent afforded the crude product which was purified by flash chromatography (ethyl acetate/petroleum ether 50/50). Removal of excess eluent furnished the product as a pale yellow oil (0.81 g, 82%): ^{1}H NMR ($CDCl_3$) δ 1.96 - 2.16 (m, 4H); 3.47 - 3.56 (m, 3H); 3.6 (m, 1H); 4.1 - 4.28 (m, 3H); 4.46 (d, J = 6.15 Hz, 2H); 5.01 (d, J = 12.1 Hz, 1H); 5.64 (d, J = 12.1 Hz 1H); 7.22 - 7.76 (m, 11H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 22.9; 28.7; 46.4; 46.9; 59.9; 67.0; 75.1; 86.0; 94.8; 117.7; 119.6; 120.1; 124.9; 127.9; 129.8; 134.9; 140.8; 141.3; 143.5; 153.0; 154.1; 166.7. IR (Nujol): cm^{-1} 3282, 3000-2800, 1713, 1610, 1533, 1451, 1220, 1058, 908, 735, 647 MS: m/e (relative intensity) 631 ([M+2], 1), 196 (5), 178 (100), 152 (5), 89 (7), 70 (10). HRMS Calculated for $C_{30}H_{26}Cl_3N_3O_6$:

629.0887. Found: 629.0887. $[a]^{25}_{D}$ = + 58.7° (c = 0.5, CHCl3).

(11S,11aS)-8-amino-11-hydroxy-10-N-(2′,2′,2′-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (150)

The protected carbinolamine **149** (0.8 g, 1.3 mmol) was added to a 5% solution of piperidine in CH_3CN (12 mL, 5 eq. of piperidine). The mixture was allowed to stir for 12 hours, extracted with water (2 x 50 mL) and the organic phase was evaporated under reduced pressure to yield a pale yellow oil (0.24 g, 50%): ^1H NMR (270 MHz, $CDCl_3$) δ 1.9 - 2.2 (m, 4H); 3.45 - 3.7 (m, 3H); 4.26 (d, J =12.1 Hz, 1H); 4.55 (m, 3H); 5.18 (d, J = 12.1 Hz, 1H); 5.61 (d, J = 10.3 Hz, 1H); 6.61 (s, 1H); 6.69 (d, J = 7.3 Hz, 1H); 7.56 (d, J = 8.2 Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.0; 28.7; 46.3; 59.8; 74.9; 95.1; 114.8; 116.5; 130.4; 135.3; 154.4; 167.3. IR (Nujol): cm^{-1} 3340, 3224, 3000-2800, 1714, 1602, 1460, 1311, 1208, 1141, 1061, 826, 759, 665. MS: m/e (relative intensity) 407 ($M^{+\cdot}$, 40), 381 (5), 340 (10), 309 (25), 161 (100), 134 (15), 105 (15), 70 (80). HRMS Calculated for $C_{15}H_16C_13N_3O_4$: 407.0206. Found: 407.0206. $[a]^{25}_{D}$ = + 47.8° (c = 0.5, CHCl3).

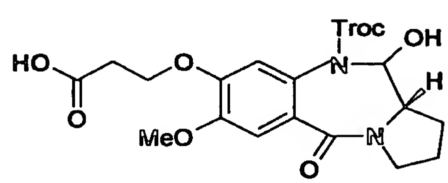
Synthesis of (11aS)-8-amino-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (151)

Cd/Pb couple (5 eq, 0.34 g) was added portion wise to a vigorously stirred solution of 150 (0.2 g, 0.5 mmol) in THF (10 mL) and aqueous ammonium acetate (10 mL). Stirring was allowed to continue for a further 2 hours at room temperature and the

reaction mixture was poured into ethyl acetate (100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to yield the crude product which was subjected to flash chromatography (silica gel, 5% MeOH, 95% $CHCl_3$). Removal of excess eluent afforded the product as a white solid (26 mg, 53% yield): ^1H NMR (270 MHz, $CDCl_3$, CD_3OD) δ 1.6 - 2.2 (m, 4H); 3.2 - 3.4 (m, 2H); 3.5 (m, 1H); 5.0 (m, 2H); 6.05 (m, 1H); 6.25 (m, 1H); 7.43 (m, 1H), 7.75 (m, 1H). IR (Nujol): cm-1 3304, 3000-2800, 1613, 1457, 1377, 1244, 1202, 1122, 1072, 825, 759, 721. MS: m/e (relative intensity) 215 ($M^{+\cdot}$, 100), 186 (15), 178 (10), 146 (10), 119 (25), 91 (15),70 (30), 65 (5). HRMS Calculated for $C_{12}H_13N_3O$: 215.1058. Found: 215.1059. $[a]^{25}$ = + 163.3° (c = 0.2, $CHCl_3$).

Example 4: Synthesis of the C8-Amines

Synthesis of 3-(11-Hydroxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-2-propenylpropanoate (159) (see Figure 21)



Nitro Di-acid (153)

14.63 g of (4-carboxy-2-methoxy-5hydroxy-phenoxy) propanoic acid **152** (61 mmol) was added portionwise to 70% nitric acid (100 mL) stirred at 0°C. The reaction was stirred for 1 h at 0°C then

allowed to return to rt. The reaction mixture was then poured onto ice and allowed to stir for 18 h. The solids were then collected by filtration and washed with water. The aqueous layer was then extracted with ethyl acetate (3 x 150 mL). The organics were then washed with water and brine and dried with sodium sulphate. The solvent was then removed *in vacuo* to give **153** as a yellow solid, yield = 14.01 g (83%) mp 141 °C. ^{1}H NMR ($CDCl_3$): δ 8.51 (bs, 2H, COO**H**), 7.57 (s, 1H, C**H**CNO_2), 7.15 (s, 1H, CH_3OCC**H**), 4.35 (t, 2H, J =6.41 Hz, CH_2**CH_2**O), 3.99 (s, 1H, OC**H_3**), 2.86 (t, 2H, J = 6.41 Hz, C**H_2**CH_2O). ^{13}C-NMR ($CDCl_3$): δ 33.93 (**C**H_2CH_2O), 56.42 (O**C**H_3), 65.20 (CH_2**C**H_2O), 108.27 (NO_2C**C**H), 111.26 (CH_3OC**C**H), 122.50 (**C**COOH), 141.14(**C**NO_2), 149.21 (CH_2CH_2O**C**), 152.40 (CH_3O**C**), 166.93 (arom. **C**OOH), 172.24 (aliph. **C**OOH). IR (Nujol) ν 2860, 2620, 1740, 1720, 1590, 1540, 1480, 1390, 1350, 1290, 1230, 1250, 1200, 1060 cm^{-1}. EIMS *m/e* (relative intensity) : 286 ($M^{+\cdot}$, 20), 241 (10), 213 (100), 169 (20), 152 (5), 111 (20), 96 (5), 79 (5), 73 (15), 55 (10). HRMS Calcd. for $C_{11}H_{14}NO_8$ = 285.0511 found = 285.0538.

2-Propene 3-(4-carboxy-2-methoxy-5-nitrophenoxy)propanoate (154)

A mixture of 3-(4-carboxy-2-methoxy-5-nitrophenoxy)propanoic acid (**153**) (20 g, 74.3 mmol) and *p*-toluene sulphonic acid monohydrate (2.3 g, 7.4 mmol) in allyl alcohol (240 mL, 3.5 mol) was refluxed for 7 h then allowed to cool. The allyl alcohol was then removed *in vacuo*, and the residue triturated with dilute HCl acid and collected by filtration. This solid was taken up in EtOAc, and the resulting solution washed with water and brine and dried over sodium sulphate. Evaporation *in vacuo* afforded **154** as a white

solid (19.27 g, 84%): mp 128-130 °C; ^{1}H-NMR ($CDCl_3$): δ 2.92 (t, 2H, J = 6.35 Hz); 3.94 (s, 3H); 4.38 (t, 2H, J = 6.41 Hz); 4.65 (d, 2H, J = 5.61 Hz); 5.27 (dd, 1H, J_1 = 1.28 Hz, J_2 = 19.42 Hz); 5.33 (dd, 1H, J_1 = 1.28 Hz, J_2 = 17.04 Hz); 5.92 (m, 1H); 7.15 (s, 1H); 7.45 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 34.1, 56.5, 65.0, 65.4, 108.5, 111.3, 118.3, 122.9, 131.8, 141.1, 149.1, 152.6, 167.1, 170.0; IR (Nujol); ν 1730, 1630, 1550, 1430, 1390, 1290, 1230, 1190, 1170, 1070, 1030, 1010 cm^{-1}; MS (EI) m/z (relative intensity): 325 ($M^{+\cdot}$, 19), 251 (3), 213 (2), 196 (3), 211 (3), 113 (19), 91 (4), 71 (9), 55 (6); HRMS: calcd. for $C_{14}H_{15}NO_8$ 325.0798, found 232.0773.

Prop-2-enyl 4-(*N*-2*S*-Diethylthiomethylpyrrolidinecarboxy)-2-methoxy-5-nitrophenoxy)propanoate (155)

2-Propene 3-(4-carboxy-2-methoxy-5-nitrophenyloxy)propanoate (**154**): 5 g, 15.34 mmol), oxalyl chloride (2 mL, 23 mmol) and 5 drops of DMF were stirred in dry THF (100 mL) for 18 h. The solvent was then removed *in vacuo* and the residue dissolved in dry THF (50 mL). This was added dropwise to a vigorously stirred mixture of (2s)-pyrrolidone-2-caroxaldehyde diethyl thioacetate(3.15 g, 15.34 mmol) and triethylamine (1.86 g, 18.41 mmol). The stirring was continued for 18 h. The solvent was then removed *in vacuo* and the product purified by flash chromatography eluting with ethyl acetate to give **155** (7.48g, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.74 (s, 1H, OCC**H**C), 6.83 (s, 1H, MeOCC**H**C), 5.98-5.86 (m, 1H, $CH_2C\mathbf{H}CH_2$, 5.33 (d, 1H, J = 26.56 Hz, $OCH_2CHC\mathbf{H_2}$), 5.28 (d, 1H, J = 20.24 Hz, $OCH_2CHC\mathbf{H_2}$), 4.88 (d, 1H, J = 3.85 Hz, NCHC**H**), 4.74-4.65 (m, 2H, $OC\mathbf{H_2}CHCH_2$) 4.42

(t, 2H, J = 7.69 Hz, $CH_2\mathbf{CH_2}OC$), 3.94 (s, 3H, $O\mathbf{CH_3}$), 3.29-3.21 (m, 2H, $N\mathbf{CH_2}$), 2.96 (p, 2H, J =3 .12 Hz, $\mathbf{CH_2}CH_2O$), 2.87-2.67 (m, 4H, $S\mathbf{CH_2}CH_3$), 2.32-1.78 (m, 4H, $NCH_2\mathbf{CH_2CH_2}$)1.38-1.31 (m, 6H, $SCH_2\mathbf{CH_3}$). ^{13}C-NMR ($CDCl_3$): δ 15.00, 15.13 ($SCH_2\mathbf{CH_3}$), 24.63 ($NCH_2CH_2\mathbf{CH_2}$), 26.28, 26.59, 27.22 ($NCH_2\mathbf{CH_2}CH_2$), 34.13 ($\mathbf{CH_2}CH_2O$), 50.19 ($\mathbf{NCH_2}$), 52.80 (NCH**CH**), 56.60 ($O\mathbf{CH_3}$), 61.08 (N**CH**), 65.13 ($CH_2\mathbf{CH_2}O$), 65.64 ($O\mathbf{CH_2}CHCH_2$), 108.70 (arom. **CH**), 109.47 (arom. **CH**), 118.55 ($OCH_2CH\mathbf{CH_2}$), 128.58 (**C**CON), 131.73 ($OCH_2\mathbf{CH}CH_2$), 137.17 ($\mathbf{C}NO_2$), 147.98 ($CH_2CH_2O\mathbf{C}$), 154.57 ($\mathbf{C}OCH_3$), 166.61 (**CO**N), 170.14 (**CO**O). IR (Nujol) ν= 3550-2720, 3000, 2630, 2200, 1740, 1640, 1580, 1530, 1340, 1280, 1220, 1180, 1050 cm^{-1}. MS (EI): m/e (relative intensity): 527 ($M^{+\cdot}$, 1), 377 (10), 310 (12), 309 (72), 308 (94), 268 (20), 142 (4). HRMS calcd. for $C_{24}H_{35}O_7N_2S_2$ = 527.1875, found = 527.1885.

5-Amino-3-(4-(2-diethylthiomethyl-(2S)-perhydro-1-pyrroloylcarbonyl)-2-methoxyphenyloxy)2-propenylpropanoate (156)

8 (7.21 g, 14.05 mmol) and Tin(II) chloride (15.85 g, 76 mmol) was refluxed for 40 min in ethyl acetate (100 mL) then allowed to cool. The solvent was then removed *in vacuo* and the residue was triturated with saturated bicarbonate solution at 0°C. EtOAc (50 mL) was added and the reaction stirred overnight. The reaction mixture was then filtered through Celite and the filter cake washed with ethyl acetate. The combined organics were then washed with water and brine, dried with sodium sulphate and the solvent removed *in vacuo*. The product was purified using flash chromatography eluting with 5% MeOH in dichloromethane to give a yellow oil, yield = 5.87g (86%). ^{1}H NMR ($CDCl_3$): δ 6.82 (s, 1H,

arom. CH), 6.28 (s, 1H, arom.CH), 5.99-5.85 (m, 1H, OCH_2CHCH_2), 5.31 (dd, 1H, J = 1.28 Hz, 27.66 Hz, OCH_2CHCH_2), 5.26 (dd, 1H, J = 1.28 Hz, 20.70 Hz, OCH_2CHCH_2), 4.71-4.62 (m, 5H, including doublet at 4.62, 2H, J = 5.49 Hz, NH_2 + NCHCH, OCH_2CHCH_2), 4.27 (t, 2H, J = 6.59 Hz, CH_2CH_2O), 3.92, (m, 1H, NCH), 3.74 (s, 3H, OCH_3), 3.66-3.57 (m, 2H, NCH_2) 2.89 (t, 2H, J = 6.6 Hz, CH_2CH_2O), 2.83-2.64 (m, 4H, SCH_2CH_3), 2.28-1.80 (m, 4H, $NCH_2CH_2CH_2$), 1.25 (m, 6H, SCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.20 (SCH_2CH_3), 26.55, 27.23 ($NCH_2CH_2CH_2$), 34.27 (CH_2CH_2O), 53.20 (NCHCH), 56.08 (OCH_3), 60.10 (NCH), 60.39 (NCH_2), 64.20 (CH_2CH_2O), 64.41 (OCH_2CHCH_2), 102.26 (arom. CH), 113.71 (arom. CH), 118.40 (OCH_2CHCH_2), 131.93 (OCH_2CHCH_2), 141.03 (CNH_2), 141.74 (CH_2CH_2OC), 154.56 ($COCH_3$), 169.69 (CON), 170.53 (COO). IR (neat liquid film) 3500-3000, 3460, 3400, 2970, 1740, 1650, 1535, 1470, 1345, 1290, 1225, 1190 cm^{-1}; MS (EI): m/e (relative intensity): 482 ($M^{+\cdot}$, 4), 347 (2), 278 (31), 137 (1), 70 (3); HRMS calcd. for $C_{23}H_{34}O_5N_2S_2$ = 482.1909, found = 482.1925.

3-(4-(2-Diethylthiomethyl-(2S)-perhydro-1-pyrrolylcarbonyl)-2-methoxy-5-(2,2,2-trichloroethyloxycarbonylamino)phenyloxy)2-propenylpropanoate (157)

To a solution of **156** (5.67g, 11.74 mmol) in dichloromethane (200 mL) was added pyridine (2.02 mL, 23.48 mmol). To this was added dropwise at 0°C a solution of trichloroethyl chloroformate (1.616 mL, 11.74 mmol). The solution was stirred for a further 1 hour at 0°C. The organics were washed with 1 N HCl (3 X 100 mL), water (3 x 100 mL) brine (100 mL), dried over magnesium sulphate and the solvent removed *in vacuo* to give a brown oil (6.8g, 88%)

^1H NMR ($CDCl_3$): δ 9.14 (bs, 1H, N**H**), 7.88 (bs, 1H, C**H**CNH), 6.93 (s, 1H, MeOCC**H**C), 5.99-5.86 (m, 1H, OCH_2C**H**CH_2), 5.31 (dt, 1H, J =1.47 Hz, 27.84 Hz $OCH_2CHC\mathbf{H_2}$), 5.25 (dt, 1H, J =1.29 Hz, 21.61 Hz, $CH_2CHC\mathbf{H_2}$), 4.89-4.77 (m, 4H, including doublet 1H, J =1.28 Hz, CHC**H**SEt, N**H**, $C\mathbf{H_2}$-TrOC), 4.62 (d, 2H, J =1.28 Hz, $OC\mathbf{H_2}CHCH_2$), 3.81 (s, 3H, $OC\mathbf{H_3}$), 3.60 (m, 2H, $NC\mathbf{H_2}$), 2.91 (d, 2H, J =6.42 Hz, $CH_2C\mathbf{H_2}O$), 2.84-2.61 (m, 4H, $SC\mathbf{H_2}CH_3$), 1.37-1.23 (m, 6H, $SCH_2C\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$): δ 170.33 (ester **C**O), 168.50 (**C**ON), 151.94 (O**C**O), 150.29 (**C**OCH_3), 144.52 (**C**OCH_2CH_2), 131.93 (OCH_2**C**HCH_2), 131.35 (**C**NH), 118.29 (OCH_2**C**HCH_2), 112.21 (arom. **C**H), 105.51 (arom. **C**H), 95.27 (**C**Cl_3), 76.24 (**C**H_2TrOC), 74.39 (**C**H_2TrOC), 65.42 (CH_2**C**H_2O), 61.14 (N**C**H), 56.30 (O**C**H_3), 53.00 (NCH**C**HSEt), 34.27 (**C**H_2CH_2O), 27.30, 26.71, 26.43, 25.24 ($NCH_2CH_2CH_2$), 15.27, 14.87, 14.18 (SCH_2CH_3). MS (EI): m/e (relative intensity): 658, 656 ($M^{+\cdot}$, 1), 508 (1), 373 (6), 305 (5), 304 (27), 192 (5), 70 (12).

3-(11-Hydroxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-a][1,4]diazepin-8-yloxy-2-propenylpropanoate (158)

A solution of **157** (6.8g, 10.34 mmol) in acetonitrile/water (4:1, 200 mL) was treated with calcium carbonate (2.585g, 25.85 mmol) and mercuric(II) chloride (7.00g, 25.85 mmol) and the solution was stirred for 18 h. The reaction was then filtered through Celite and the filter pad washed with ethyl acetate. The organics were collected and washed with water (3 x 50 mL), brine (100 mL) and dried over magnesium sulphate. The solvent was removed *in vacuo* and the resulting product was purified by flash chromatography eluting with ethyl acetate to give the product as

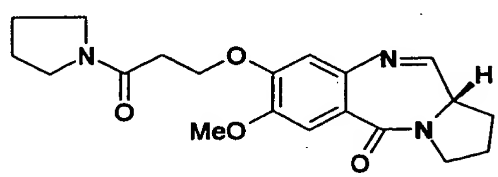
a yellow oil (3.67 g, 64%) ^{1}H NMR ($CDCl_3$): δ 7.25 (arom. **CH**), 6.86 (s, 1H, arom. CH), 6.00-5.85 (m, 1H, CH_2**C**HCH_2), 5.67 (d, 1H, J = 9.71 Hz, TrOC-**CH$_2$**) 5.37-5.20 (m, 3H, TrOC-**CH$_2$** + OCH_2CH**CH$_2$**), 4.65 (d, 2H, J = 5.67 Hz, CH_2CHC**H$_2$**O), 4.36-4.22 (m, 3H, CH_2**CH$_2$**O + NC**H**OH), 3.90 (s, 3H, OC**H$_3$**), 3.72-3.47 (m, 3H, NC**H** + NC**H$_2$**), 2.91 (t, J = 6.41 Hz, CH_2CH_2O) 2.29-2.00 (m, 4H, NCH_2**CH$_2$CH$_2$**) ^{13}C NMR ($CDCl_3$): δ 170.33 (ester carbonyl **C**O), 166.17 (**C**ON), 154.4 (O**C**O), 149.88 (**C**OCH_3), 148.93 (**C**OCH_2CH_2), 131.86 (CH_2**C**HCH_2), 127.48 (arom. **C**N), 126.24 (**C**CON), 118.42 (OCH_2CH**C**H$_2$), 114.48 (arom. **C**H), 110.82 (arom. **C**H), 95.09 (**C**Cl$_3$), 86.42 (N**C**HOH), 74.96 (TrOC-**C**H$_2$), 65.47 (O**C**H$_2CHCH_2$), 64.43 (CH_2**C**H$_2$O), 60.13 (N**C**H), 56.14 (O**C**H$_3$), 46.44 (N**C**H$_2$), 34.26 (**C**H$_2CH_2O$), 28.64 (NCH_2CH_2**C**H$_2$),MS (EI) m/z (relative intensity): = 552 (M^+ 10), 550 (10), 374 (2), 368 (5), 304 (15), 192 (8), 70 (24), 55(24). HRMS calcd. for $C_{22}H_{25}N_2O_8Cl_3$ = 552.0651, found 3 peaks due to chlorine 552.0646, 550.676, 554.0617.

3-(11-Hydroxy-5-oxo-7-methoxy-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxypropanoic acid (159)

A solution of **158** (3.5 g, 6.35 mmol) was dissolved in ethanol (100 mL). To this was added Tetrakis(triphenylphospine)palladium(0) (350 mg, 0.303 mmol) and the solution refluxed for 30 minutes until the reaction was complete by TLC monitoring. The reaction was then allowed to cool and the filtered through Celite. The EtOH was then removed *in vacuo* to give the crude material as a yellow solid which was

used directly in the next steps. ^{1}H-NMR ($CDCl_3$): δ 7.22 (s,1H, OCC**H**CN), 7.01 (s, 1H, MeOCC**H**C), 6.27 (bs, COO**H**), 5.67 (d, 1H, J =9.5 Hz, TrOC-C**H**$_2$), 5.06 (d, 1H, J =12.09 Hz, TrOC-C**H**$_2$), 4.29-4.11 (m, 2H, C**H**OH), 3.85 (s, 3H, OC**H**$_3$), 3.71 (t, 2H, J =6.97 Hz, CH_2C**H**$_2$O), 3.51 (m, 1H, NC**H**), 2.80 (m, 2H, NC**H**$_2$), 2.12-1.99 (m, 4H, NCH_2C**H**$_2$C**H**$_2$), 1.21 (t, 2H, J =6.96 Hz, C**H**$_2$$CH_2$O) ^{13}C NMR ($CDCl_3$): δ = 174.27 (acid **C**H), 167.34 (**C**ON), 154.20 (O**C**O), 149.78 (**C**OCH$_3$), 148.74 (**C**OCH2CH2), 133.79 (arom. **C**H), 132.16 (arom. **C**H), 128.66 (arom. **C**N), 125.87 (**C**CON), 95.06 (**C**Cl$_3$), 86.53 (NCH**C**HOH), 74.95 (**C**H$_2$-TrOC), 60.67 (N**C**H), 58.24 (CH_2**C**H$_2$O), 56.04 (O**C**H$_3$), 46.44 (N**C**H$_2$), 35.24 (NCH_2**C**H$_2$$CH_2$), 28.59 ($NCH_2CH_2$**C**H$_2$), 23.08 (**C**H$_2$$CH_2$O)

Example 4(a):3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-a][1,4]diazepin-8-yloxy)-1-perhydro-1-pyrrolyl-1-propanone (161)(see Figure 22)



3-(11-Hydroxy-7-methoxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-1-perhydro-1-pyrrolyl-1-propanone (160)

To a solution of **159** (100 mg, 0.196 mmol) in dichloromethane was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04

mmol) and the solution stirred for 1h. To the reaction was added pyrrolidine (16.36 mg, 0.23 mmol) and the reaction stirred for a further 2h. The solvent was then removed *in vacuo* and the compound purified by flash chromatography eluting with 5% methanol in dichloromethane to give the product as a yellow oil, yield = 56 mg, 51%. ^{1}H NMR ($CDCl_3$): δ 7.25 (OCC**H**), 6.90 (s, 1H, MeOCC**H**C), 5.66 (d, 1H, J = 5.49 Hz, TrOC-C**H₂**), 5.16 (d, 1H, J = 12.09 Hz, TrOC-C**H₂**), 4.84-4.74 (m, 2H, C**H**OH, C11a**H**), 4.35-4.23 (m, 2H, CH_2CH_2O), 3.90 (s, 3H, OC**H₃**),), 3.73-3.67 (m, 1H, NC**H**), 3.53-3.44 (m, 6H C-ring NC**H₂**, pyrrolidine- N(C**H₂**)₂), 2.92-2.76 (m, 2H CH_2CH_2O), 2.11-1.85 (8H, C-ring $NCH_2CH_2CH_2$ + pyrrolidine-$NCH_2CH_2CH_2$); ^{13}C-NMR ($CDCl_3$): δ 168.62 (amide **C**O), 167.05 (**C**ON), 154.31 (O**C**O), 149.94 (**C**OCH₃), 148.56 (**C**OCH₂CH₂), 127.76 (arom. **C**N), 125.95 (**C**CON), 114.14 (arom. **C**H), 110.49 (arom. **C**H), 95.04 (**C**Cl₃), 86.48 (NCH**C**HOH), 74.98 (**C**H₂-TROC), 65.15 (CH_2CH_2O), 60.20 (N**C**H), 56.13 (O**C**H₃), 46.85, 46.44, 45.76, 34.47, 28.60, 26.02, 24.42 (various N-(X)**C**H₂), 23.04 (CH_2CH_2O); FABMS m/z (relative intensity) 564 (M^+ 1), 550(3), 549 (2), 548 (8), 547 (2), 546 (8), 279 (2), 192 (4), 126 (18), 98 (6).

3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-perhydro-1-pyrrolyl-1-propanone (161)

Method A. To a solution of **160** (100 mg, 0.164 mmol) in dichloromethane (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) and pyrrolidine (14 mg, 0.2 mmol) and the reaction stirred for 18 h. The mixture was then dilute with dichloromethane (100 mL) and washed with

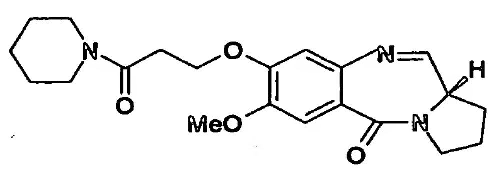
water (3 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL) and brine (50 mL). The solvent was removed *in vacuo* and the product purified by flash chromatography eluting with 5% methanol in dichloromethane to give the product **161** as a white solid (yield 26.3 mg, 40%)

Method B. To a solution of **160** (100 mg, 0.164 mmol) in dichloromethane (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (38 mg, 0.2 mmol) and the reaction stirred for 3 hours. The reaction was then treated with tetrabutylammonium fluoride (200 μL of a 1.0 M solution in THF, 0.2 mmol) and stirred for 30 min. The reaction was then treated with pyrrolidine (14 mg, 0.2 mmol) and stirred for 18 h. The mixture was then dilute with dichloromethane (100 mL) and washed with water (3 x 50 mL), saturated sodium bicarbonate solution (3 x 50 mL) and brine (50 mL). The solvent was removed *in vacuo* and the product purified by flash chromatography eluting with 5% methanol in dichloromethane to give the product **161** as a white solid (yield = 54.2 mg, 82%)

Method C: To a solution of **160** (56 mg, 0.1 mmol) in THF (3 mL) was added 1 M ammonium acetate solution (2 mL) and the reaction mixture stirred. To the solution was added 10% Cd/Pb couple (0.5 mmol, 62.4 mg) and the reaction was stirred for 90 min. The reaction was filtered and diluted with ethyl acetate (20 mL). The solution was dried with magnesium sulphate and the solvent removed *in vacuo*. the product as then purified by flash chromatography eluting with 5% methanol in dichloromethane to

give the compound as a white solid (yield = 21 mg, 56%). ^1H NMR ($CDCl_3$): δ 7.66 (m, 1H, J = 4.39 Hz, N=CH), 7.50 (s, 1H, arom. CH), 6.88 (s, 1H arom. CH), 4.42 (t, 2H, J = 6.96 Hz, $OOCCH_2CH_2$), 3.92 (s, 3H, OCH_3), 3.90-3.44 (m, 5H, pyrrolidine CH_2+NCH), 2.87 (t, 2H, 5.96 Hz, $OOCCH_2CH_2$), 2.28-2.33 (m, 2H, NCH_2CH_2), 2.10-1.87 (m, 8H, C-ring +pyrrolidine CH_2). 168.58 (amide CO), 164.65 (CON), 162.43 (imine CH), 150.52 ($COCH_3$), 147.61 ($COCH_2CH_2$), 140.76 (arom. CN), 120.33 (CCON), 111.54 (arom. CH), 110.61 (arom. CH), 65.20 ($COCH_2CH_2$), 56.21 ($COCH_3$), 53.7 (NCH), 46.77, 46.67, 45.69, 34.40, 29.62, 26.06, 24.54, (CH_2), 24.19 ($COCH_2CH_2$) MS (EI): m/e (relative intensity): 371 ($M^{+\cdot}$, 10), 246 (10), 245 (5), 231 (3), 126 (18), 98 (2), 70 (5), 55 (3); HRMS calcd. for $C_{20}H_{15}O_4N_3$ = 371.1845, found 371.1788.

Example 4(b): 3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-piperidino-1-propanone (163) (see Figure 22)



3-(11-Hydroxy-7-methoxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-1-perhydro-1-piperidino-1-propanone (162)

To a solution of **159** (100 mg, 0.196 mmol) in dichloromethane was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04

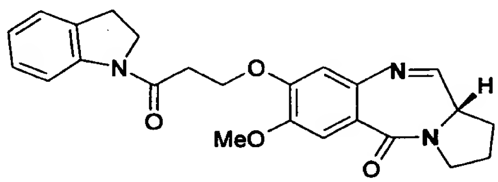
mmol) and the solution stirred for 1h. To the reaction was added piperidine (25 µL, 0.23 mmol) and the reaction stirred for a further 2h. The solvent was then removed *in vacuo* and the compound purified by flash chromatography eluting with 5% methanol in dichloromethane to give the product as a yellow oil, yield = 94 mg, 84%). ^{1}H-NMR ($CDCl_3$): δ 7.25 (s,1H, OCC**H**CN), 6.90 (s, 1H, MeOCC**H**C), 5.65 (d, 1H, J = 9.71 Hz, TrOC-C**H$_2$**), 5.17 (d, 1H, J = 11.94 Hz, TrOC-C**H$_2$**), 4.37-4.24 (m, 4H, **CHOH** + CH_2**CH_2**O), 3.91 (s, 3H, OC**H$_3$**), 3.73-3.67 (m, 1H, NC**H**), 3.54-3.45 (m, 6H, NC**H$_2$**, piperidine-N(C**H$_2$**)$_2$), 2.99-2.83 (m, 2H, C**H$_2$**CH_2O), 2.13-2.00 (m, 4H, NCH_2C**H$_2$**C**H$_2$**) 1.67-1.56 (m, 6H, piperidine-C**H$_2$**); ^{13}C NMR ($CDCl_3$): δ 168.22 (amide **C**O), 167.11 (**C**ON), 154.38 (O**C**O), 149.96 (**C**OCH_3), 148.57 (**C**OCH_2CH_2), 127.74 (arom. **C**N), 125.94 (**C**CON), 114.19 (arom. **C**H), 110.44 (arom. **C**H), 95.02 (**C**Cl_3), 86.38 (NCH**C**HOH), 74.96 (**C**H_2-TROC), 65.38 (CH_2**C**H_2O), 60.33 (N**C**H), 56.08 (O**C**H_3), 46.77 , 46.44, 42.75, 32.73, 28.60, 26.33, 25.48, 24.44 (various N-(X)CH_2), 23.05 (CH_2CH_2O); MS (EI) m/z (relative intensity): = 579 (1), 577 (1), 331 (1), 278 (1), 246 (1), 192 (4), 140 (32), 113 (2), 112 (2), 97 (1), 84 (3), 77 (3), 70 (7), 69 (4), 55 (4), HRMS calcd. for $C_{24}H_{30}N_3O_7Cl_3$ = 579.1120 found 579.1066

3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-piperidino-1-propanone (163)

To a solution of **162** (94 mg, 0.162 mmol) in THF (3 mL) was added 1 M ammonium acetate solution (2 mL) and the reaction mixture stirred. To the solution was added 10% Cd/Pb couple (0.81 mmol,

100 mg) and the reaction was stirred for 90 min. The reaction was filtered and diluted with ethyl acetate (20 mL). The solution was dried with magnesium sulphate and the solvent removed *in vacuo*. the product as then purified by flash chromatography eluting with 5% methanol in dichloromethane to give the compound as a white solid (yield = 25 mg, 39%). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, 1H, J = 4.4 Hz, N=C**H**), 7.51 (s, 1H, OCC**H**CN), 6.89 (s, 1H, MeOCC**H**C), 4.42 (t, 2H, J = 7.14 Hz, CH_2**CH_2**O), 3.93 (s, 3H, OC**H_3**), 3.90-3.44 (m, 5H, NC**H**, NC**H_2**, piperidine-N(C**H_2**)$_2$), 2.73 (t, 2H, J = 7.32 Hz C**H_2**CH_2O), 2.33-2.29 (m, 2H, C-ring CH_2), 2.11-2.02 (m, 2H, C-ring C**H_2**), 1.62-1.59 (m, 6H, piperidine C**H_2**), ^{13}C NMR ($CDCl_3$): δ 168.19 (amide **C**O), 164.66 (imine **C**H), 162.43 (**C**ON), 150.52 (**C**OCH_3), 147.61 (**C**OCH_2CH_2), 140.70 (arom. **C**N), 120.31 (**C**CON), 111.51 (arom. **C**H), 110.58 (arom. **C**H), 65.44 (CH_2**C**H_2O), 56.11 (**O**CH_3), 53.73 (N**C**H), 46.70, 46.39, 42.69, 32.72, 29.62, 26.38, 25.52, 24.40 (various N-(X)**C**H_2), 24.19 (**C**H_2CH_2O); MS (EI): m/e (relative intensity): 385 ($M^{+\cdot}$, 6), 246 (8), 245 (3), 231 (3), 140 (15), 138 (5), 97 (5), 84 (3); HRMS calcd. for $C_{21}H_{27}O_4N_3$ = 385.2002, found 385.2058.

Example 4(c): 1,(2,3-dihydro-1*H*-indolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-a][1,4]diazepin-8-yloxy)-1-propanone (165) (see Figure 22)



1-(2,3-Dihydro-1*H*-1-indolyl)-3-(11-hydroxy-7-methoxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-1-propanone (164)

To a solution of **159** (100 mg, 0.196 mmol) in DMF was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) and the solution stirred for 1h. To the reaction was added indoline (27.4 mg, 0.23 mmol) and the reaction stirred for a further 8h. The solvent was then removed *in vacuo* and the compound purified by flash chromatography eluting with 5% methanol in dichloromethane to give the product as a yellow oil (yield = 71 mg, 61%). ^{1}H-NMR ($CDCl_3$): δ 1.99-2.12 (m, 4H, $NCH_2\mathbf{CH_2CH_2}$), 3.20 (t, J = 8.42 Hz, $\mathbf{CH_2}CH_2O$), 3.71-5.00, (m, 4H, $N\mathbf{CH_2}$, N**CH**, **CH**OH), 3.89 (s, 3H, $O\mathbf{CH_3}$), 4.18-4.09 (m, 2H, indole-CH_2), 4.27 (d, 2H, J = 11.90 Hz, indole-CH_2), 4.43 (t, J = 6.23 Hz, $CH_2\mathbf{CH_2}O$), 5.16 (d, 1H, J = 11.91 Hz, TrOC-CH_2), 5.30 (s, 1H, OH), 5.66 (d, 1H, J = 9.89 Hz, TrOC-CH_2), 7.20-6.93 (m, 5H, indole-CH, arom CH), 8.18 (d, 1H, J = 8.25 Hz, indole-CH); ^{13}C-NMR ($CDCl_3$): δ 168.24 (**CON**), 166.97 (**CON**), 154.36 (OCO), 149.91, **C**OCH$_3$), 148.65 (**C**OCH$_2$CH$_2$),

132.14, 131.99 (indolyl ring junction), 128.61, 128.43 (indole-CH), 127.52, (arom. CN), 124.61 (**C**CON), 114.20 (arom. **C**H), 110.58 (arom. **C**H) 95.02 (**C**Cl_3), 86.43 (NCH**C**HOH), 75.01 ((TrOC-CH), 64.89 (CH_2CH_2O), 60.13 (N**C**H), 56.11 (O**C**H_3), 48.11 (indole-CH_2), 46.43 (N**C**H_2), 35.64, 28.64, 27.97, (CH_2), 23.03 (**C**H_2CH_2O); MS (EI) m/z (relative intensity): = 595 (M^+ 1), 415 (1), 365 (1), 246 (2), 192 (13), 174 (11), 173 (7), 119 (17), 118 (10), 70 (13).

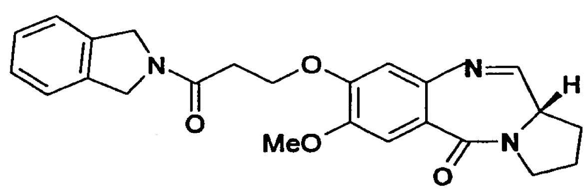
Iso-indoline (2,3,-dihydro-1*H*-isoindole) ^1H NMR ($CDCl_3$): δ 7.22 (m, 4H, arom C**H**), 4.26 (s, 4H, C**H**$_2$), 4.08 (bs, 1H, N**H**), ^{13}C NMR ($CDCl_3$): δ 140.37, 140.36 (ring junctions), 127.15, 126.90, 122.60, 122.51, 122.33 (arom. **C**H), 52.31 (**C**H_2).

1,(2,3-dihydro-1*H*-indolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (165)

To a solution of **164** (71 mg, 0.116 mmol) in THF (3 mL) was added 1 M ammonium acetate solution (2 mL) and the reaction mixture stirred. To the solution was added 10% Cd/Pb couple (0.58 mmol, 72 mg) and the reaction was stirred for 90 min. The reaction was filtered and diluted with ethyl acetate (20 mL). The solution was dried with magnesium sulphate and the solvent removed *in vacuo*. The product as then purified by flash chromatography eluting with 5% methanol in dichloromethane to give the compound as a white solid (yield = 26 mg, 54%). ^1H NMR ($CDCl_3$): δ 7.66 (d, 1H, J = 4.58 Hz, C**H**=N), 7.50 (s, arom. C**H**), 7.19 (m, 4H indolyl arom. C**H**), 6.91 (s, 1H, arom. C**H**), 4.48 (m, 2H, CH_2C**H**$_2$O), 4.18-4.19 (m, 2H, indolyl C**H**$_2$), 3.91 (s, 3H, OC**H**$_3$), 3.88-3.44 (m,

3H, NCH, +indolyl CH_2), 3.02 (t, 2H, J = 6.6 Hz, CH_2CH_2O), 2.30-2.28 (m, 2H, NCH_2), 2.17-2.05 (m, 4H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ 168.31 (amide CO), 164.61 (CON), 162.47, (imine CH), 147.59 ($COCH_2CH_2$), 140.70 (arom. CN), 127.53, 124.59, 123.87, (indolyl arom. CH), 120.44 (CCON), 117.03 (indolyl arom. CH), 11.56 (arom. CH), 110.61 (arom. CH), 64.80 ($COCH_2CH_2$), 56.14 ($COCH_3$), 53.70 (NCH), 48.11, 46.69, 35.50, 29.60, 28.67, 28.00 (CH_2), 24.19 ($COCH_2CH_2$).

Example 4(d): 1,(2,3-dihydro-1*H*-2-isoindolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-a][1,4]diazepin-8-yloxy)-1-propanone (167) (see Figure 22)



1-(2,3-dihydro-1*H*-2-isoindolyl)-3-(11-hydroxy-7-methoxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-a][1,4]diazepin-8-yloxy-1-propanone (166)

To a solution of **159** (100 mg, 0.196 mmol) in DMF was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) and the solution stirred for 1h. To the reaction was added indoline (27.4 mg, 0.23 mmol) and the reaction stirred for a further 8h. The solvent was then removed *in vacuo* and the compound purified

by flash chromatography eluting with 5% methanol in dichloromethane to give the product as a yellow oil (yield = 75 mg, 64%). ^{1}H-NMR ($CDCl_3$): δ 7.29-7.20 (m, 5H, isoindole arom. + arom.CH), 6.91 (s, 1H, arom CH), 5.66 (d, 1H, J = 9.7 Hz, TrOC-CH_2) 5.30 (s, 1H, OH), 5.19 (d, 1H, J = 9.7 Hz, TrOC-CH_2), 4.94 (m, 2H, isoindolyl CH_2), 4.79 (s, 2H, isoindolyl CH_2), 4.38 (t, 2H, J = 6.42 Hz, $CH_2\mathbf{CH_2}O$), 4.25, (d, 1H, J = 11.91 Hz, C11-H), 3.81-3.40 (2H, NCH_2), 3.03-2.85 (m, 2H, $\mathbf{CH_2}CH_2O$), 2.11-1.98 (m, 4H, $NCH_2\mathbf{CH_2CH_2}$); ^{13}C-NMR ($CDCl_3$): δ 169.17 (**C**ON), 167.02 (**C**ON), 154.27 (O**C**O), 149.91 (**C**OCH$_3$), 148.64 (**C**OCH$_2$CH$_2$), 136.19, 136.11 (isoindolyl ring junction), 128.61, 127.88 (isoindolyl **C**H), 127.78 (arom. **C**N), 127.58, (**C**CON), 114.28 (arom. **C**H), 110.54 (arom. **C**H), 95.09 (**C**Cl$_3$), 86.51 (NCH**C**HOH), 74.98 (TrOC-CH_2), 65.21 ($CH_2\mathbf{C}H_2O$), 60.23 (N**C**H), 56.05 (O**C**H$_3$), 52.14, 52.81 (isoindolyl **C**H$_2$), 46.43, (N**C**H$_2$), 34.31, 29.68, 28.60 (Nx**C**H$_2$), 23.03 ($\mathbf{C}H_2CH_2O$); FABMS m/z (relative intensity): = 612 (1), 596 (1), 594 (1), 279 (1), 192 (1), 174 (8), 146 (5), 118 (13), 91 (2), 55 (3). FABHRMS found compound minus OH i.e. $C_{27}H_{27}N_3O_6Cl_3$ = 595.1044

1,(2,3-dihydro-1*H*-2-isoindolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (167)

To a solution of **166** (75 mg, 0.122 mmol) in THF (3 mL) was added 1 M ammonium acetate solution (2 mL) and the reaction mixture stirred. To the solution was added 10% Cd/Pb couple (0.61 mmol, 76 mg) and the reaction was stirred for 90 min. The reaction was filtered and diluted with ethyl acetate (20 mL). The solution

was dried with magnesium sulphate and the solvent removed *in vacuo*. The product was then purified by flash chromatography eluting with 5% methanol in dichloromethane to give the compound as a white solid (yield = 42.6 mg, 83%). ^1H NMR ($CDCl_3$): δ 7.66 (d, 2H, J = 4.39 Hz, N=CH), 7.48 (s, 1H, arom. CH), 7.30 (s, 4H, indolyl arom. CH), 6.89 (s, 1H, arom. CH), 4.48 (t, 3H, J = 6.59 Hz, $COCH_2CH_2$), 3.84 (s, 3H, OCH_3), 3.81-3.69 (m, 2H, indolyl CH_2), 3.61-3.51 (m, 1H, NCH), 2.97 (p, 5H, J = 6.9 Hz, CH_2CH_2O), 2.32-2.28 (m, 2H, NCH_2), 2.30-2.01 (m, 4H, $NCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ169.29 (amide CO), 164.66 (imine CH), 162.52 (CON), 150.45 ($COCH_3$), 147.63 ($COCH_2CH_2$), 140.57, (arom. CN), 127.86, 127.56, 123.04, 122.62 (indolyl arom. CH), 120.38 (CCON), 111.52 (arom. CH), 110.53 (arom. CH), 65.16 ($COCH_2CH_2$), 56.06 ($COCH_3$), 53.73 (NCH), 52.16, 50.64, 46.70, 34.22, 29.57 (CH_2), 24.18 ($COCH_2CH_2$); MS (EI): m/e (relative intensity): 419 ($M^{+\cdot}$, 21), 416 (2), 415 (2), 246 (10), 245 (3), 231 (3), 174 (4); HRMS calcd. for $C_{24}H_{25}O_4N_3$ = 419.1845, found 419.1821.

Examples 5 to 8 : Cytotoxicity Data

NCI *In Vitro* Cytotoxicity Studies

The National Cancer Institute (NCI), Bethesda, Maryland, USA has available an *in vitro* cytotoxicity screen which consists of approximately 60 human tumour cell lines against which compounds are tested at a minimum of five concentrations each differing 10-fold. A 48 hour continuous exposure protocol is used, where cell viability or growth is estimated with an SRB protein assay.

Method

The test compounds were evaluated against approximately 60 human tumour cell lines. The NCI screening procedures were described in detail by Monks and co-workers (Monks, A *et al.*, Journal of the National Cancer Institute, 1991, 83, 757). Briefly, cell suspensions were diluted according to the particular cell type and the expected target cell density (5000-40,000 cells per well based on cell growth characteristics), and added by pipette (100 μL) into 96-well microtitre plates. The cells were allowed a preincubation period of 24 h at 37°C for stabilisation. Dilutions at twice the intended test concentration were added at time zero in 100 μL aliquots to the wells. The test compounds were evaluated at five 10-fold dilutions (10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} μM). The test compounds were incubated for 48 h in 5% CO_2 atmosphere and 100% humidity. The cells were then assayed using the sulphorhodamine B assay. A plate reader was used to read the optical densities and a microcomputer processed the readings into LC_{50} values, which is the dosage required to kill half of the cells.

The results presented in examples 5 to 8 are LC_{50} values which are below 10μM, which is taken to be the dividing line between cytotoxicity and non-cytotoxicity.

NCI Hollow Fibre Assay for Preliminary *In Vivo* Testing

The Biological testing Branch of the Developmental Therapeutics Program of the NCI has adopted a preliminary *in vivo* screening

tool for assessing the potential anticancer activity of compounds identified by the large scale *in vitro* cell screen. For these assays, human tumour cells are cultivated in polyvinylidene (PVDF) hollow fibres, and a sample of each cell line is implanted into each of two physiologic compartments (intraperitoneal and subcutaneaous) in mice. Each test mouse received a total of 6 fibres (3 intraperitoneally and 3 subcutaneously) representing 3 distinct cancer cell lines. These mice are treated with potential antitumour compounds at each of 2 test doses by the intraperitoneal route using a QD x 4 treatment schedule. Vehicle controls consist of 6 mice receiving the compound diluent only. The fibre cultures are collected on the day following the last day of treatment. To assess anticancer effects, the viable cell mass is determined for each of the cell lines using a formazyn dye (MTT) conversion assay. From this, the %T/C can be calculated using the average optical density of compound treated samples divided by the average optical; density of the vehicle controls. In addition, the net increase in cell mass can be determined for each sample as a sample of fibre cultures are assessed for viable cell mass on the day of implantation into mice. Thus, the cytostatic and cytocidal capacities of the test compound can be assessed.

Generally, each compound is tested against a minimum of 12 human cancer cell lines. This represents a total of 4 experiments since each experiment contains 3 cell lines. The data are reported as %T/C for each of the 2 compound doses against each of the cell lines with separate values calculated for the

intraperitoneal and subcutaneous samples.

Compounds are selected for further *in vivo* testing in standard subcutaneous xenograft models on the basis of several hollow fibre assay criteria. These include: (1) a %T/C of 50 or less in 10 of the 48 possible test combinations (12 cell lines X 2 sites X 2 compound doses); (2) activity at a distance (intraperitoneal drug/subcutaneous culture) in a minimum of 4 of the 24 possible combinations; and/or (3) a net cell kill of 1 or more of the cell lines in either implant site. To simplify evaluation, a points system has been adopted which allows rapid viewing of the activity of a given compound. For this, a value of 2 is assigned for each compound dose which results in a 50% or greater reduction in viable cell mass. The intraperitoneal and subcutaneous samples are scored separately so that criteria (1) and (2) can be evaluated. Compounds with a combined IP + SC score of 20, a SC score of 8 or a net cell kill of one or more cell lines are refereed for xenograft testing. This comparison indicated that there was a very low probability of missing an active compound if the hollow fibre assay were used as the initial *in vivo* screening tool. In addition to these criteria, other factors (e.g. unique structure, mechanism of action) may result in referral of a compound for xenograft testing without the compound meeting these criteria.

<u>Example 5: *In Vitro* Cytotoxicity of compounds of formula I</u>

All of the compounds synthesised in example 1, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC50;μM) are

set out below, and are illustrated in Figure 23.

TUMOUR TYPE	CELL-LINE DESIGNATION	UP2003 (**24**)	UP2051 (**31**)	UP2052 (**33**)	UP2065 (**42**)
Lung	NCI-H23		9.3		
	NCI-H460	7.6		3.0	
	NCI-H522			3.1	
Colon	COLO 205	1.4			4.0
	HCC-2998	5.2	5.2	0.8	
	HCT-116			1.1	
	KM12	9.5			
CNS	SNB-75	6.0			
Melanoma	MALME-3M	0.7	5.1		4.7
	M14			2.7	
	SK-MEL-2		7.6	0.5	3.5
	UACC-62	0.7			
Renal	786-0			3.0	
	RXF 393		0.8		0.8
Breast	MDA-MB-435				0.8

Of the compounds tested, the above showed cytotoxicity against human lung, colon, CNS, melanoma, renal and breast cancer cell lines. Replacing the C-8 benzyloxy group in UP2003 (**24**) with a methoxy substituent (UP2065, **42**) significantly changed the cytoxicity profile, activity was lost against lung, CNS, and colon cancer cell lines (only reduced activity against Colo 205 remained). However, additional cytotoxic activity was gained against the melanoma cell line SKMEL-2, the renal cell line RXF-393 and the breast cell line MDA-MB-435. Reduction of the ester moiety in UP2003 (**24**) to afford the alcohol UP2052 (**33**) resulted in increased activity in the lung cancer cell line NCI-460 and the colon cell line HCC-2998. Additional activity was registered against the lung cell line NCI-H522, the colon cell line HCT-116, the melanoma cell line M14 and the renal cancer cell line 786-0.

Interestingly, the acetylated analogue UP2051 (**31**) exhibited attenuated or abolished activity in these cell lines (e.g. 7.6μM verses 0.5 μM for UP2052 in the melanoma SK-MEL-2 cell line.

Example 6(a): *In Vitro* Cytotoxicity of compounds of formula II

All of the compounds synthesised in example 2, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC50;μM) are set out below, and are illustrated in Figure 24.

TUMOUR TYPE	CELL-LINE DESIGNATION	UP2064 (**74**)	UP2001 (**80**)	UP2004 (**70**)	UP2023 (**64**)	UP2067 (**172**)
Lung	NCI-H23			7.6		
	NCI-H226				9.1	
	NCI-H460		2.7			
	NCI-H522				5.2	5.0
Colon	COLO 205	0.6		3.9	5.8	5.8
	HCC-2998		0.099	5.5	7.0	
	KM12				7.1	
CNS	SF-539				9.4	6.8
	SNB-75		7.5			5.4
Melanoma	MALME-3M	0.9	0.073		7.8	7.4
	M14					0.8
	SK-MEL-2	1.7			7.4	
	SK-MEL-28	2.6			8.4	6.6
	SK-MEL-5			7.8	6.0	
	UACC-257	7.4		7.3		
	UACC-62	0.6	0.077	5.3	7.2	3.0
Renal	RXF 393	0.8			6.1	0.8
Breast	MDA-MB-435	2.3			7.6	0.8
	MDA-N			9.0	6.6	0.6

Of the compounds tested, the above listed exert their cytotoxic effect (LC_{50}) most strongly in the Lung, Colon, CNS. Melanoma, Renal and Breast cell line panels. Within the group, it is apparent that exchanging a C-8 benzyloxy substituent (UP2004, **70**) for a methoxy group (UP2064, **74**) results in increased activity in

the Melanoma panel. The methoxy analogue is more potent and acts against a greater number of cell lines. The methoxy analogue also exhibits improved activity against the colon cancer cell line Colo 205 and, in addition, the methoxy analogue exhibits activity against the renal cell line RXF-393 which is not observed with the benzyloxy compound. Replacing the electron rich dimethoxy A-ring with for an iodo substituted aromatic ring (UP2023, **64**) resulted in slight attenuation of activity in some cell lines, but the analogue showed activity against a wider spread of cell lines (i.e. 5 melanoma cell lines against only 3 for the benzyloxy analogue). Changing the nature of the C-ring ex0-unsaturation from an alkene to a ketone (UP2067, **172**) lead to additional activity against the breast cancer cell line MDA-MB-435, renal cell line RXF-393, the melanomas MALME-3M, M14, SKMEL-28, the CNS cancers SF-539 and SNB-75 and against the lung cell line NCI-H522.

The PBD dimer UP2001 (**80**) exhibited potent and selective cytoxicity activity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75 and the melanoma cell lines MALME-3M (very potent, 0.08 μM) and UACC-62 (very potent, 0.07 μM), which may be attributable to its ability to cross link DNA.

<u>Example 6(b): Hollow Fibre Assay on Compounds of formula II</u>

Two of the compounds tested underwent the NCI Hollow Fibre Assay, and the results are presented below.

	UP2001 (**80**)	UP2004 (**70**)
IP score	40	8
SC score	14	10
Total score	54	18
Cell Kill	Y	N

UP2001 (**80**) and UP2004 (**70**) were subjected to the NCI Hollow Fibre assay described above. UP2001 has been selected for xenograft studies based on its combined IP + SC score (54) which was greatly in excess of 20, and its SC score which was higher than 8. UP2004 has been selected on the basis of its SC score, it being higher than 8.

Example 7: *In Vitro* Cytotoxicity of compounds of formula III

All of the compounds synthesised in example 3, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC50;μM)are set out below, and are illustrated in Figure 25.

TUMOUR TYPE	CELL-LINE DESIGNATION	UP2026 (**136**)	UP2027 (**138**)	UP2028 (**151**)	UP2068 (**96**)
Lung	NCI-H522	7.8	8.0	0.8	8.5
Colon	COLO 205	8.8		5.0	
	HCC-2998	6.4			
	KM12			8.8	
CNS	SNB-75			8.2	
Melanoma	MALME-3M	6.1		5.7	8.3
	LOX IMVI				9.7
	M14	7.8			6.5
	SK-MEL-2	7.4	9.5	5.4	8.1
	SK-MEL-28	7.1		8.1	9.6
	SK-MEL-5	9.0			
	UACC-257	7.7			

	UACC-62	6.6			
Renal	RXF 393	7.6	6.6	0.7	6.3
Breast	HS 578T			9.2	
	MDA-MB-435	6.3		7.2	8.3
	MDA-N				6.3

The C-7-phenyl substituted compound UP2026 (**136**) showed cytotoxicity against cell lines in the human lung, colon, melanoma, renal and breast cancer cell line panels. Interestingly, unlike other PBDs the molecule was inactive in the CNS cell line panel. However, UP2026 (**136**) was active against nearly all the members of the melanoma panel. Inclusion of a methoxy group in the C7 aryl moiety (**138**) resulted in increased selectivity as cytotoxicity was only observed in the lung cell line NCI-H522, the melanoma cell line SKMEL-2 and the renal cell line RXF-393. Introduction of a nitro group at C7 completely abolished cytotoxic activity, however, it seems likely that activity would be restored once the nitro group is reduced to an amine; in this way UP2029 (**140**) might prove to be a useful prodrug. The C8 amino substituted PBD (UP2028, **151**) showed good activity in the lung, colon, CNS, melanoma, renal and breast cell line panels. On the other hand the trimethoxy PBD (UP2068, **96**) was only active in the lung, melanoma, renal and breast cell line panels.

Example 8: *In Vitro* cytotoxicity of compounds of formula IV

The compounds synthesised in example 4, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC50;μM) are set out below, and are illustrated in Figure 26.

TUMOUR TYPE	CELL-LINE DESIGNATION	UP2005 (**161**)	UP2008 (**167**)
Lung	NCI-H23		8.9
	NCI-H522	8.7	
Colon	HCC-2998		8.1
CNS	SF-295	8.8	
	SF-539	7.7	
Melanoma	MALME-3M	7.5	6.8
	LOX IMVI	9.2	
	M14	6.2	8.4
	SK-MEL-2	7.6	6.5
	SK-MEL-28	6.5	
	UACC-257		7.1
Renal	RXF 393	6.8	

Two of the four C8 PBD amides, UP2005 (**161**) and UP2008 (**167**), demonstrated cytotoxicity (LC_{50}) in the NCI assay. UP2005 (**161**) showed selectivity for the lung, CNS, melanoma and renal cancer cell in panels. The compound was particularly active in the melanoma panel exhibiting cytotoxicity against 5 out of the 8 melanoma cell lines. UP2008 (**167**) revealed a slightly different profile being active in the lung, colon, and melanoma panels. Again the molecule was particularly active in the melanoma panel.

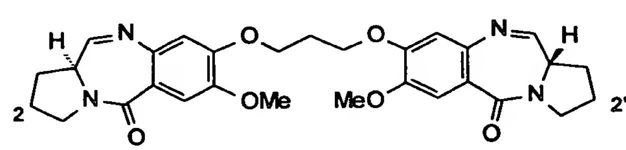
Example 9: Further results for PBD dimer SJG-136 (UP2001, 80)

The compound synthesized in example 2(d) (SJG-136, **80**) underwent some further assays.

The first assay, which is described in G.B.Jones, *et al.*, *Anti-Cancer Drug Des.*, 1990, **5**, 249, which is incorporated herein by reference, determines the effect of the test compound on the helix melting temperature of DNA. This assay is designed to give an indication of the strength and extent of cross-linking of the DNA strands by the test compound (i.e. a measure of the stabalisation of the DNA upon ligand binding).

The melting temperature is determined for a 1:5 molar ratio of [ligand][DNA], where the calf thymus DNA concentration is 100 mM in aqueous sodium phosphate buffer (10 mM sodium phosphate + 1 mM EDTA, pH 7.00 ± 0.01). For calf thymus DNA at pH 7.00 ± 0.01, the melting temperature is 67.83 ± 0.06 °C (mean value from 30 separate determinations).

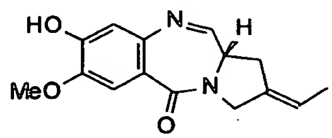
For a 1:5 molar ratio of [PBD]:[DNA], the PBD dimer **80** elevates the helix melting temperature (ΔT_m) of calf thymus DNA by an unprecedented 33.6 °C after incubation for 18 hours at 37 °C. Under identical conditions, the C-ring-unsubstituted dimer DSB-120:



DSB-120

provides a ΔT_m of 15.1°C, demonstrating the extraordinary effect of introducing C2/C2'-unsaturation. In common with other PBD dimers, **80** exerts most of its effect upon the GC-rich or high temperature regions of the DNA melting curves. In a similar fashion to DSB-120, it provides some 60-80% of its stabilising effect without prior incubation, suggesting a kinetic effect in the PBD reactivity

profile. However, the comparative ΔT_m curves show that, on a concentration basis alone, SJG-136 is ≥ 10-fold more effective than DSB-120. Even at a [PBD]:[DNA] molar ratio of 1:100, SJG-136 still exhibits significantly better DNA binding affinity than the monomer tomaymycin at a 1:5 [PBD][DNA] molar ratio.



Tomamycin

The results for a [PBD]:[DNA] ratio of 1:5 are summarised in the table below (All ΔTm values ± 0.1-0.2 °C)

Compound	Induced ΔT_m (°C) after incubation at 37 °C for		
	0 h	4 h	18 h
SJG-136 (**80**)	25.7	31.9	33.6
DSB-120	10.2	13.1	15.1
Tomamycin	0.97	2.38	2.56

The data presented in the above table show that SJG-136 (**80**) is the most potent DNA-stabilising agent known to date according to this particular assay.

The second assay determined the cytotoxicity of SJG-136 (**80**) in the human ovarian carcinoma cell line A2780 and its cisplatin-resistant subline A2780cisR, and compared this data with the cytotoxicity of the related dimer DSB-120 (see above) and Cisplatin. Relative to the parental line, the A2780cisR subline is known to have elevated GSH levels, an increased level of repair of DNA-cisplatin adducts, and a decreased ability to uptake cisplatin (M.Smellie, *et al.*, *Br. J. Cancer*, 1994, **70**, 48).

The results, which were obtained by incubating the cells with the compounds for 96 hours at 37°C, and assessing the cell number using Sulforhodamine B, are presented in the table below:

	A2780	$IC_{50}{}^{a}$ (μM) for A2780cis^{R}	RF^{b}
SJG-136 (80)	0.0000225	0.000024	1.1
DSB-120	0.0072	0.21	29.2
Cisplatin	0.265	8.4	32

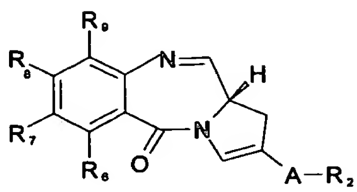
a Dose of compounds required to inhibit cell growth by 50% compared with control

b RF is the resistance factor (IC_{50} resistant/parent)

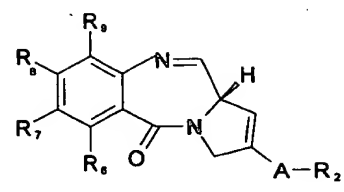
The IC_{50} value for **80** in the A2780 cell line is only 23 pM, representing a 320-fold increase in cytotoxicity compared to DSB-120 (IC_{50} = 7.2 nM). More interestingly, whereas DSB-120 has a reduced potency in the cisplatin-resistant A2780cisR (IC_{50} = 0.21 mM), SJG-136 is almost 9,000-fold more potent in this cell line with a similar IC_{50} value (24 pM) to that in the normal A2780, giving a Resistance Factor of 1.1. The fact that both DSB-120 and cisplatin give Resistance Factors of 29.2 and 32, respectively, across this pair of cell lines suggests that SJG-136 may have potential in the treatment of cisplatin-refractory disease.

CLAIMS

1. A compound of the formula Ia or Ib:



(Ia)



(Ib)

wherein:

A is CH_2, or a single bond;

R_2 is selected from: R, OH, OR, CO_2H, CO_2R, COH, COR, SO_2R, CN;

R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;

where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group;

and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above, or the compound is a dimer with each monomer being the same or different and being of formula Ia or Ib, where the R_8 groups of the monomers form together a bridge having the formula -X-R'-X- linking the monomers, where R' is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;

except that in a compound of formula Ia when A is a single bond, then R_2 is not CH=CH($CONH_2$) or CH=CH($CONMe_2$).

2. A compound of formula Ia according to claim 1, with the proviso that when A is a single bond, then R_2 is not $CH=CR^AR^B$, where R^A and R^B are independently selected from H, R^C, COR^C, $CONH_2$, $CONHR^C$, $CONR^C{}_2$, cyano or phosphonate, where R^C is an unsubstituted alkyl group having 1 to 4 carbon atoms.

3. A compound according to either claim 1 or claim 2, wherein A is CH_2.

4. A compound according to claim 3, wherein R_2 is CO_2H, CO_2R, CH_2OH, or CH_2OR.

5. A compound according to claim 4, wherein R_2 is CO_2Me, $CO_2{}^tBu$, CH_2OH, or CH_2OAc.

6. A compound according to any one of the preceding claims wherein R_6, R_7 and R_9 and, unless the compound is a dimer, R_8 are independently selected from H and OR.

7. A compound according to claim 6, wherein R_6, R_7 and R_9 and, unless the compound is a dimer, R_8 are independently selected from H, OMe and OCH_2Ph.

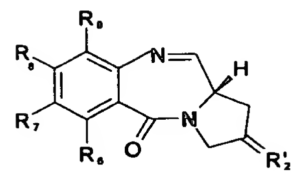
8. A compound according to claim 6, wherein R_7 and, unless the compound is a dimer, R_8 are OR, and R_6 and R_9 are H.

9. A compound according to claim 8, wherein R_7 and, unless the compound is a dimer, R_8 are independently either OMe or OCH_2Ph.

10. A compound according to any one of the preceding claims of formula Ia.

11. A compound according to any one of the preceding claims which is a dimer, wherein the dimer bridge is of the formula $-O-(CH_2)_p-O-$, where p is from 1 to 12.

12. A compound of formula II:



(II)

wherein:
R'_2 is selected from: O, CHR''_2, where R''_2 is selected from H, R, CO_2R, COR, CHO, CO_2H, halo;
R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;
where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may from part of, or be, a functional group;
and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above or the compound is a dimer with each monomer being the same or different and being of formula II, where the R_8 groups of the monomers form together a bridge having the formula -X-R'-X- linking the monomers, where R' is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;
except that:

(i) when R'_2 is CH-Et, and R_6, R_8 and R_9 are H, R_7 is not sibirosamine pyranoside; and

(ii) when R'_2 is CH-Me, and R_6 and R_9 are H, R_7 and R_8 are not both H or both OMe, or OMe and OH respectively.

13. A compound according to claim 12, wherein R'_2 is O, CH_2 or $CHCH_3$.

14. A compound according to either claim 12 or claim 13, wherein R_6, R_7 and R_9 and, unless the compound is a dimer, R_8 are independently selected from H, OR or a halogen atom.

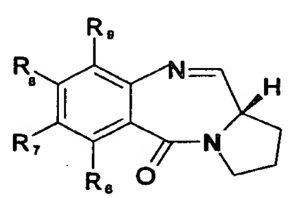
15. A compound according to claim 14, wherein R_6, R_7 and R_9 and, unless the compound is a dimer, R_8 are independently selected from H, OMe and OCH_2Ph, and I.

16. A compound according to claim 14, wherein R_7 and, unless the compound is a dimer, R_8 are independently OR or a halogen atom and R_6 and R_9 are H.

17. A compound according to claim 16, wherein R_7 and, unless the compound is a dimer, R_8 are independently selected from OMe, OCH_2Ph or I.

18. A compound according to any one of claims 12 to 17 which is a dimer, wherein the dimer bridge is of the formula $-O-(CH_2)_p-O-$, where p is from 1 to 12.

19. A compound of the formula III:



(III)

wherein:
R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;
where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may from part of, or be, a functional group;

and R_8 is selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn, where R is as defined above or the compound is a dimer with each monomer being the same or different and being of formula III, where the R_8 groups of the monomers form together a bridge having the formula -X-R'-X- linking the monomers, where R' is an alkylene chain containing from 3 to 12 carbon atoms, which chain may be interrupted by one or more hetero-atoms and/or aromatic rings and may contain one or more carbon-carbon double or triple bonds, and each X is independently selected from O, S, or N;
wherein at least one of R_6, R_7, R_8 and R_9 are not H;
except that:

(i) when R_6 and R_9 are H, R_7 and R_8 are not both OMe, OMe and OBn respectively, or OMe and OH respectively;

(ii) when R_6 and R_7 are H, R_8 and R_9 are not Me and OH respectively;

(iii) when three of R_6, R_7, R_8 and R_9 are H, the other is not Me;

(iv) when R_6, R_7, and R_8 are H, R_9 is not OMe;

(v) when R_6, R_8 and R_9 are H, R_7 is not OMe; and

(vi) when R_6, and R_9 are H and R_7 is OMe, the compound is not a dimer.

20. A compound according to claim 19, wherein only one of R_6, R_7, R_8 and R_9 is H.

21. A compound according to claim 20, wherein those of R_6, R_7, R_9 and, unless the compound is a dimer, R_8 which are not H are OR.

22. A compound according to claim 21, wherein those of R_6, R_7, R_9 and, unless the compound is a dimer, R_8 which are not H are selected from OMe, and OBn.

23. A compound according to either claim 19 or claim 20, wherein at least one of R_6, R_7, R_8 and R_9 is a dimer, is NH_2.

24. A compound according to claim 19, claim 20 or claim 23, wherein at least one of R_6, R_7, R_8 and R_9 is an aryl group, preferably of up to 12 carbon atoms, which is optionally substituted

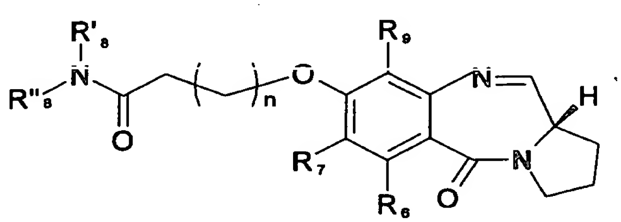
by one or more halo, hydroxy, amino, or nitro groups, and optionally contains one or more hetero atoms which may from part of, or be, a functional group.

25. A compound according to claim 24, wherein at least one of R_6, R_7, R_8 and R_9, is a phenyl group, optionally substituted by one or more methoxy, ethoxy or nitro groups.

26. A compound according to claim 25, wherein at least one of R_6, R_7, R_8 and R_9, is selected from: Ph, p-MeO-Ph, m-NO_2-Ph and p-NO_2-Ph.

27. A compound according to any one of claims 19 to 26 where the compound is a dimer, wherein the dimer bridge is of the formula -O-$(CH_2)_p$-O-, where p is from 1 to 12.

28. A compound of formula IV:



(IV)

wherein:
R_6, R_7 and R_9 are independently selected from H, R, OH, OR, halo, amino, NHR, nitro, Me_3Sn;
where R is a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally containing one or more hetero atoms which may form part of, or be, a functional group;
R_8' and R_8" are either independently selected from H, R or together form a cyclic amine; and
n is from 1 to 7.

29. A compound according to claim 28, wherein R_7 is an electron withdrawing group.

30. A compound according to either claim 28 or claim 29, wherein R_6 and R_9 are selected from H and OR.

31. A compound according to claim 30, wherein R_6 and R_9 are selected from OMe, OEt and OBn.

32. A compound according to any one of claims 28 to 31, wherein n is 1 to 3.

33. A compound according to any one of the preceding claims wherein R is selected from a lower alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms, or an aryl group of up to 12 carbon atoms, optionally substituted by one or more halo, hydroxy, amino, or nitro groups.

34. A compound according to claim 33, wherein R is selected from a lower alkyl group having 1 to 10 carbon atoms optionally substituted by one or more halo, hydroxy, amino, or nitro groups.

35. A compound according to claim 34, wherein R is an unsubstituted straight or branched chain alkyl having 1 to 10 carbon atoms.

36. The use of a compound according to any one of the preceding claims in a method of therapy.

37. A pharmaceutical composition comprising a compound according to any one of claims 1 to 35 and a pharmaceutically acceptable carrier or diluent.

38. The use of a compound according to any one of claims 1 to 35 to prepare a medicament for the treatment of a gene-based disease.

39. The use of a compound according to any one of claims 1 to 35 to prepare a medicament for the treatment of a viral, parasitic or bacterial infection.

40. A process for preparing a compound according to any one of claims 1 to 35.

41. The use of a compound according to any one of claims 1 to 35 for the preparation of a medicament for the treatment of cisplatin-refactory disease.

42. A method of inhibiting the growth of cisplatin-refactory cells which method comprises treating said cells with a compound according to any one of claims 1 to 35.

43. A method according to claim 42 wherein said compound is SJG-136 1,1'-[[(Propane-1,3-diyl)dioxy]bis[(11a*S*)-7-methoxy-2-methylidene-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one].

Figure 1

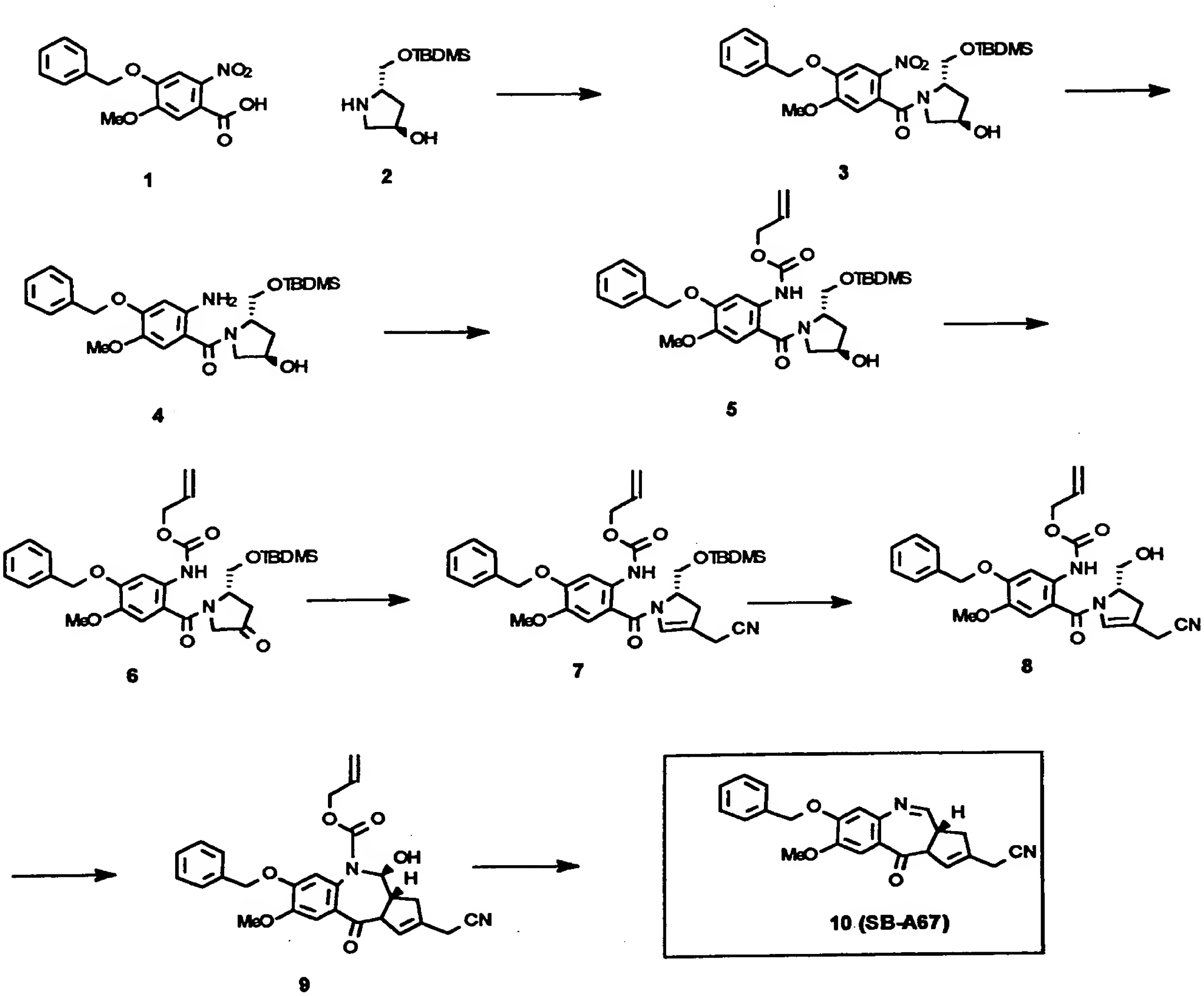
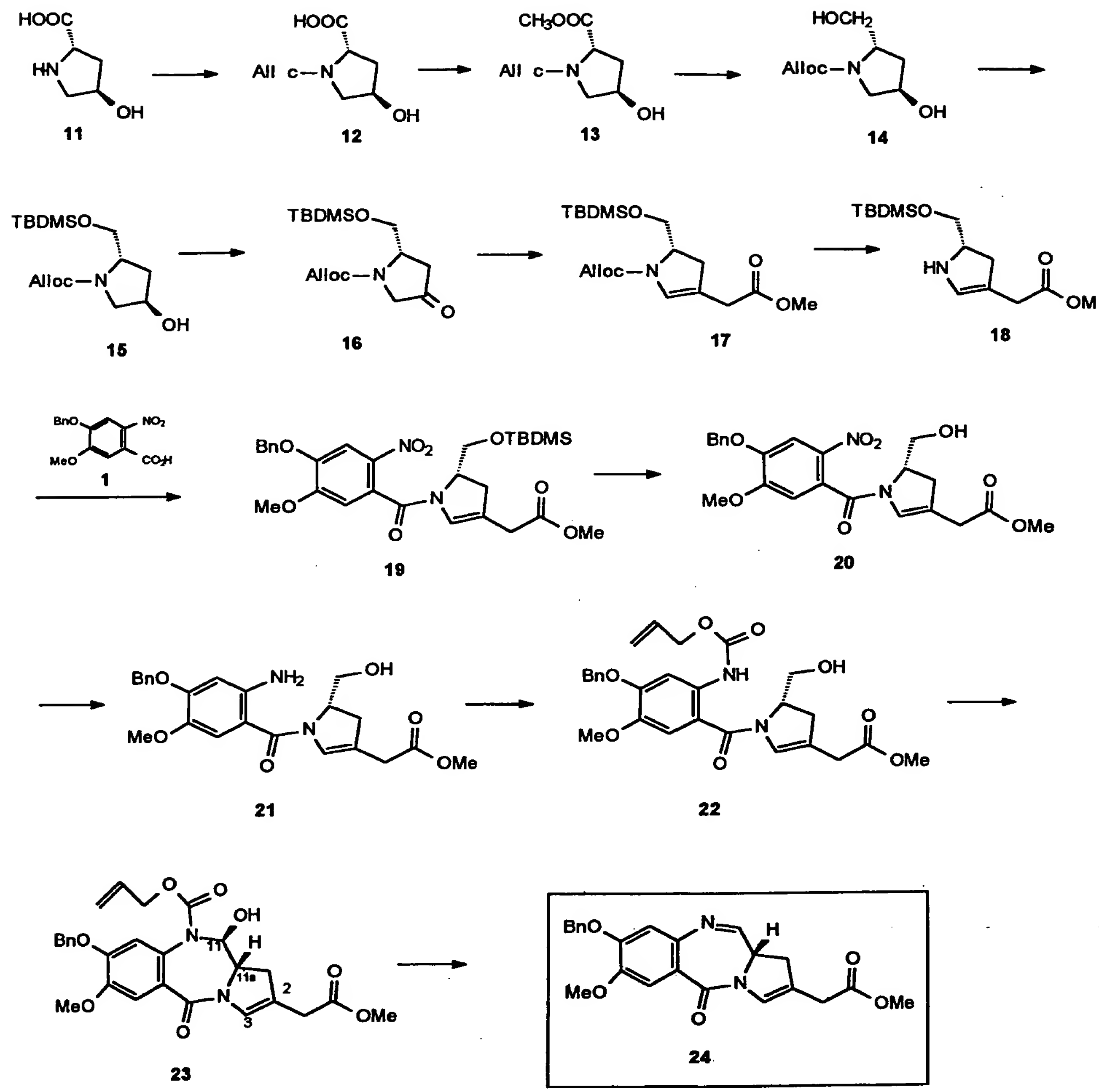
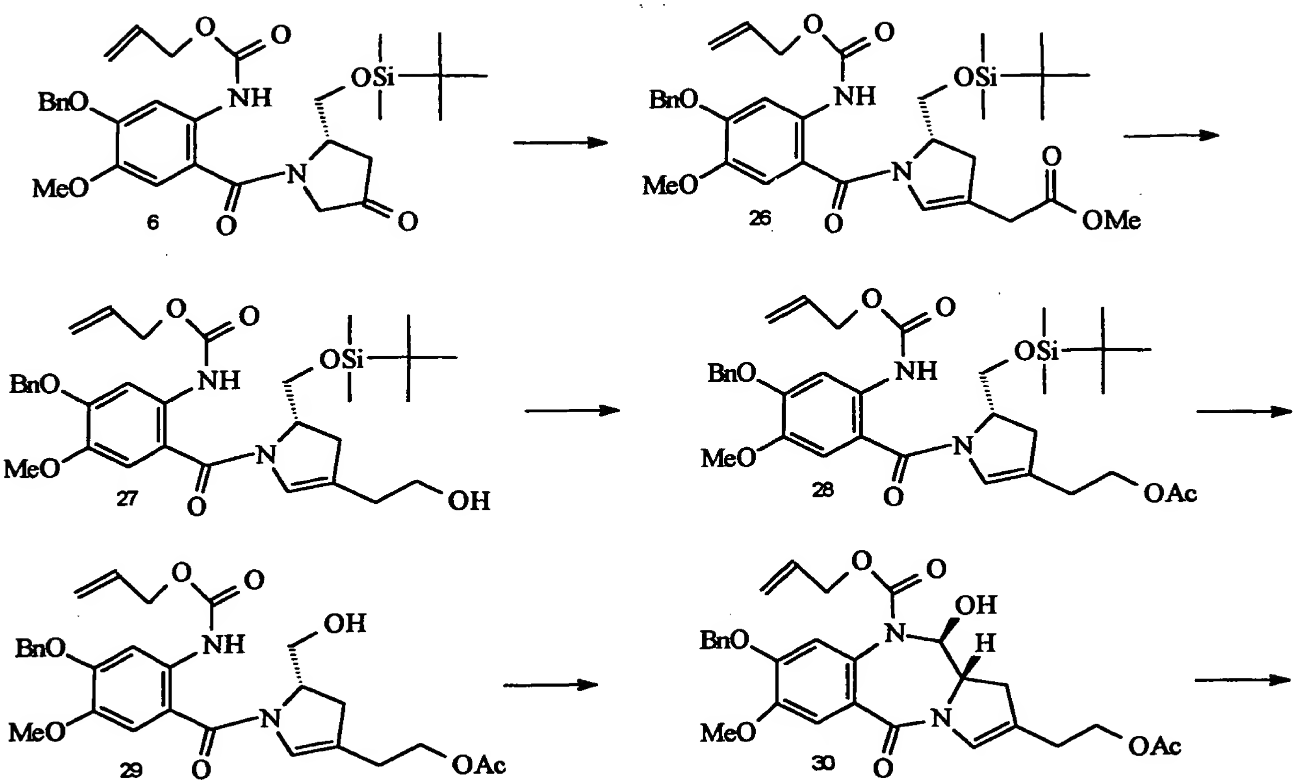


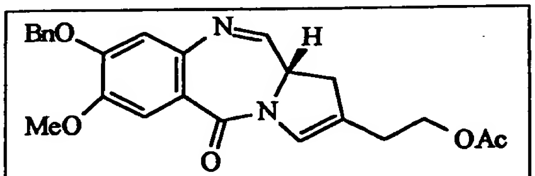
Figure 2



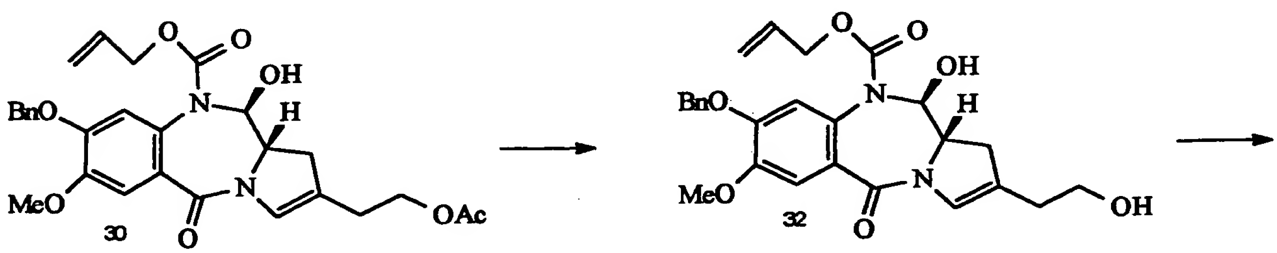
11
12
13
14
15
16
17
18
1
19
20
21
22
23
24
TBDMSO
Alloc
OTBDMS
BnO
MeO
OMe

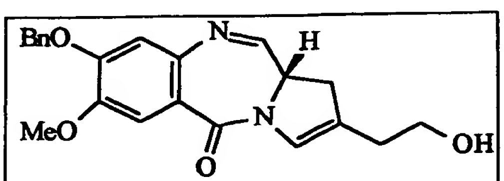
Figure 3





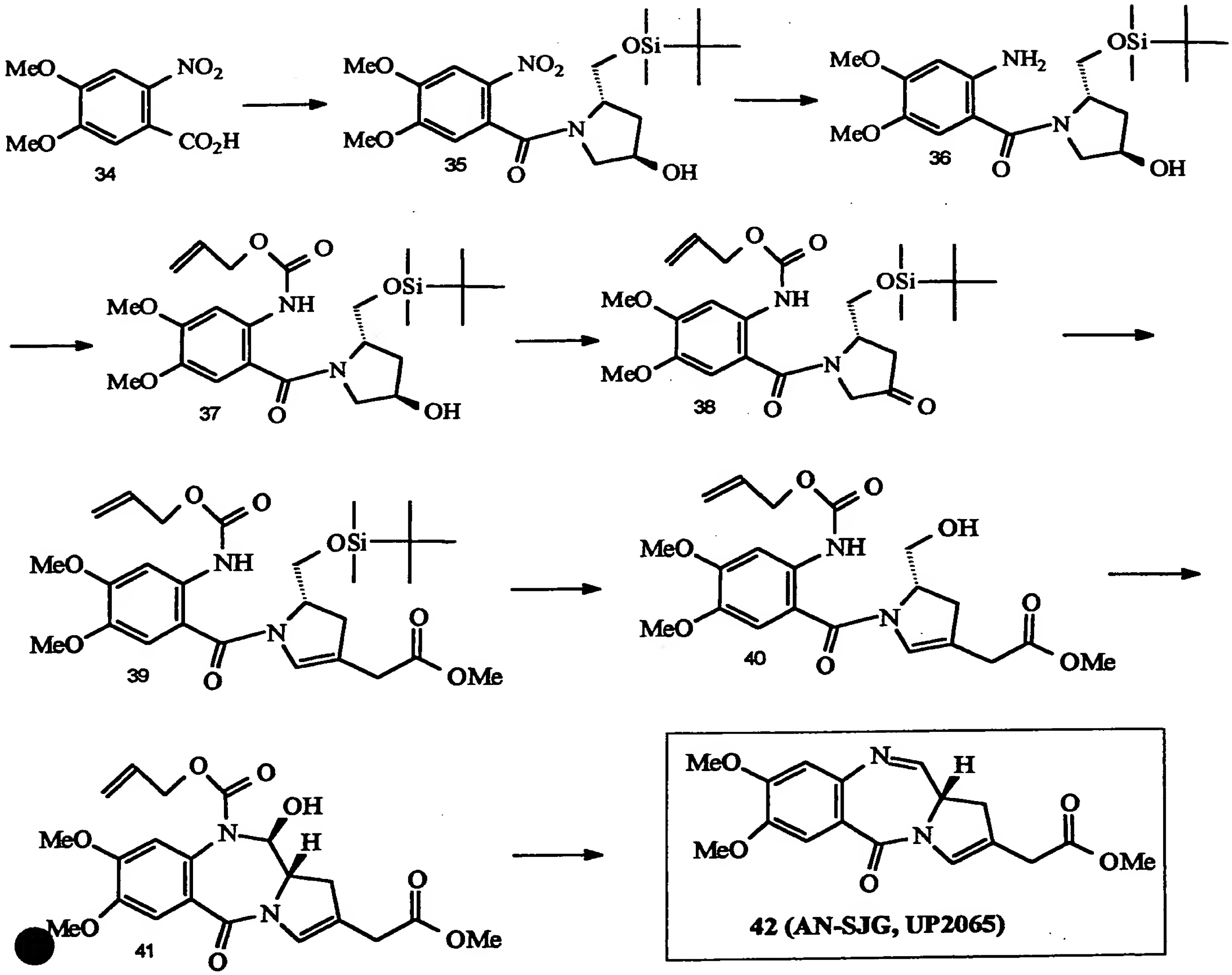
31 (SJG-30, UP2051)





33 (SJG-303, UP2052)

Figure 4



MeO
NO2
MeO
CO2H
34
OSi
35
OH
NH2
36
O
NH
37
38
39
OMe
40
41
N
H
42 (AN-SJG, UP2065)

Figure 5

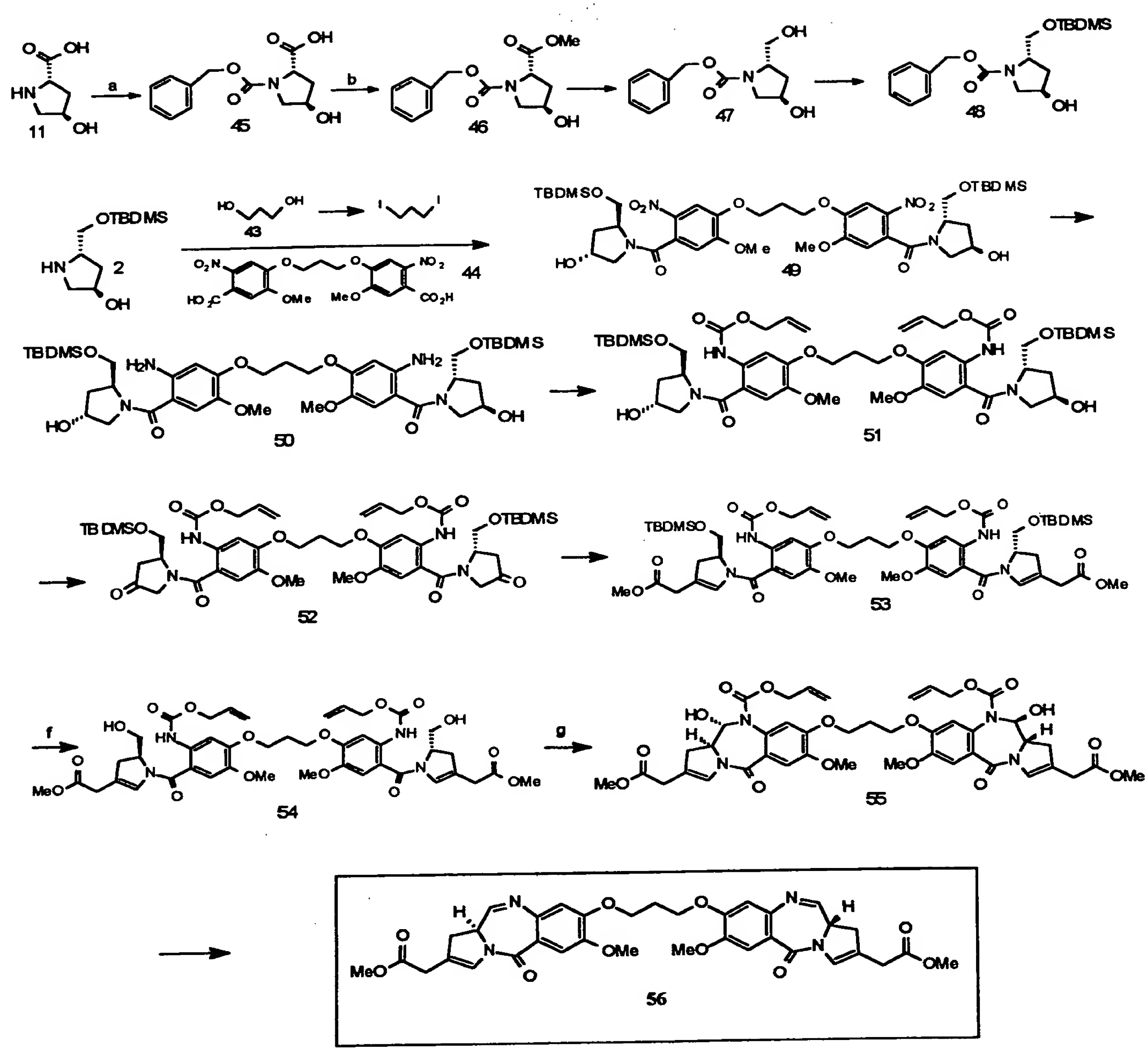
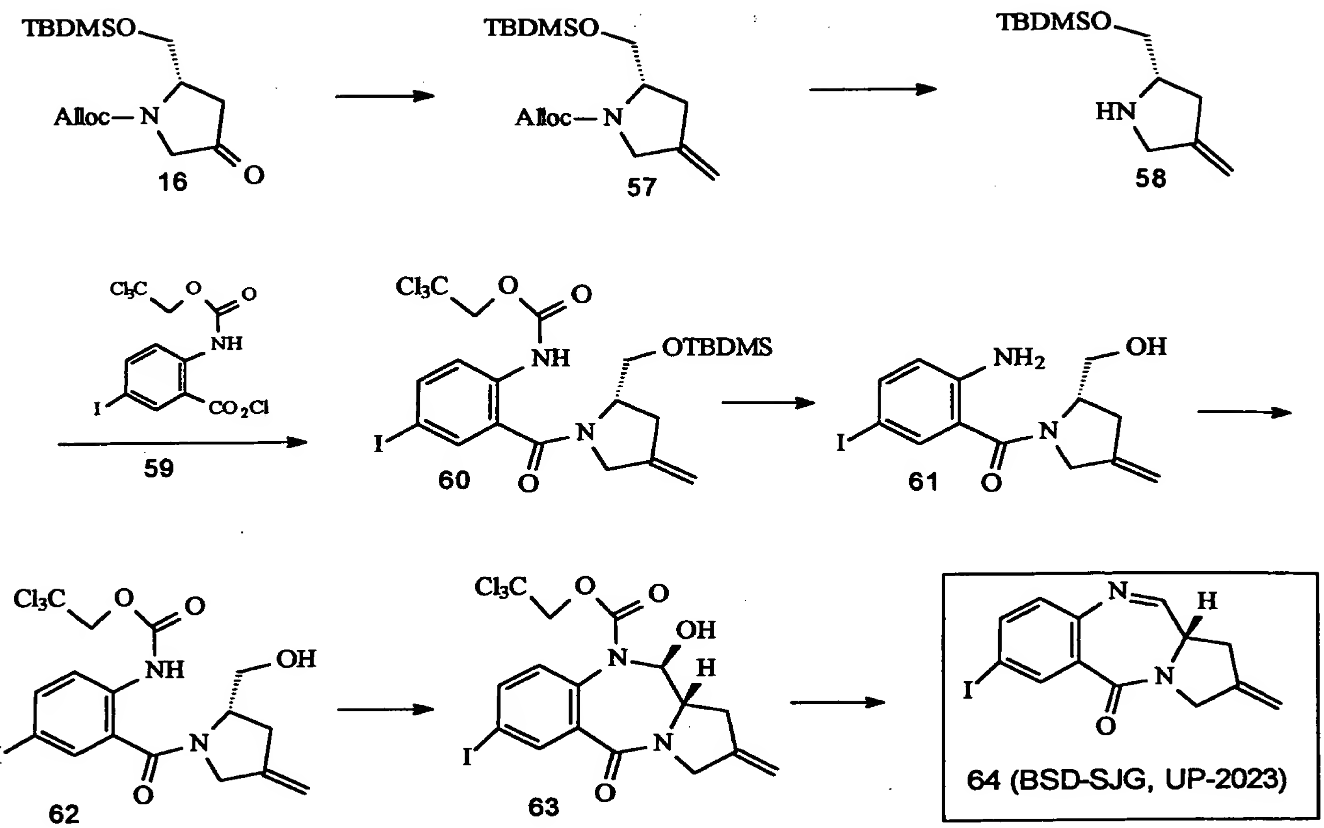


Figure 6


TBDMSO
Alloc—N
16
O
TBDMSO
Alloc—N
57
TBDMSO
HN
58
Cl3C
O
O
NH
I
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59
Cl3C
O
O
NH
OTBDMS
I
N
60
O
NH2
OH
I
N
61
O
Cl3C
O
O
NH
OH
I
N
62
O
Cl3C
O
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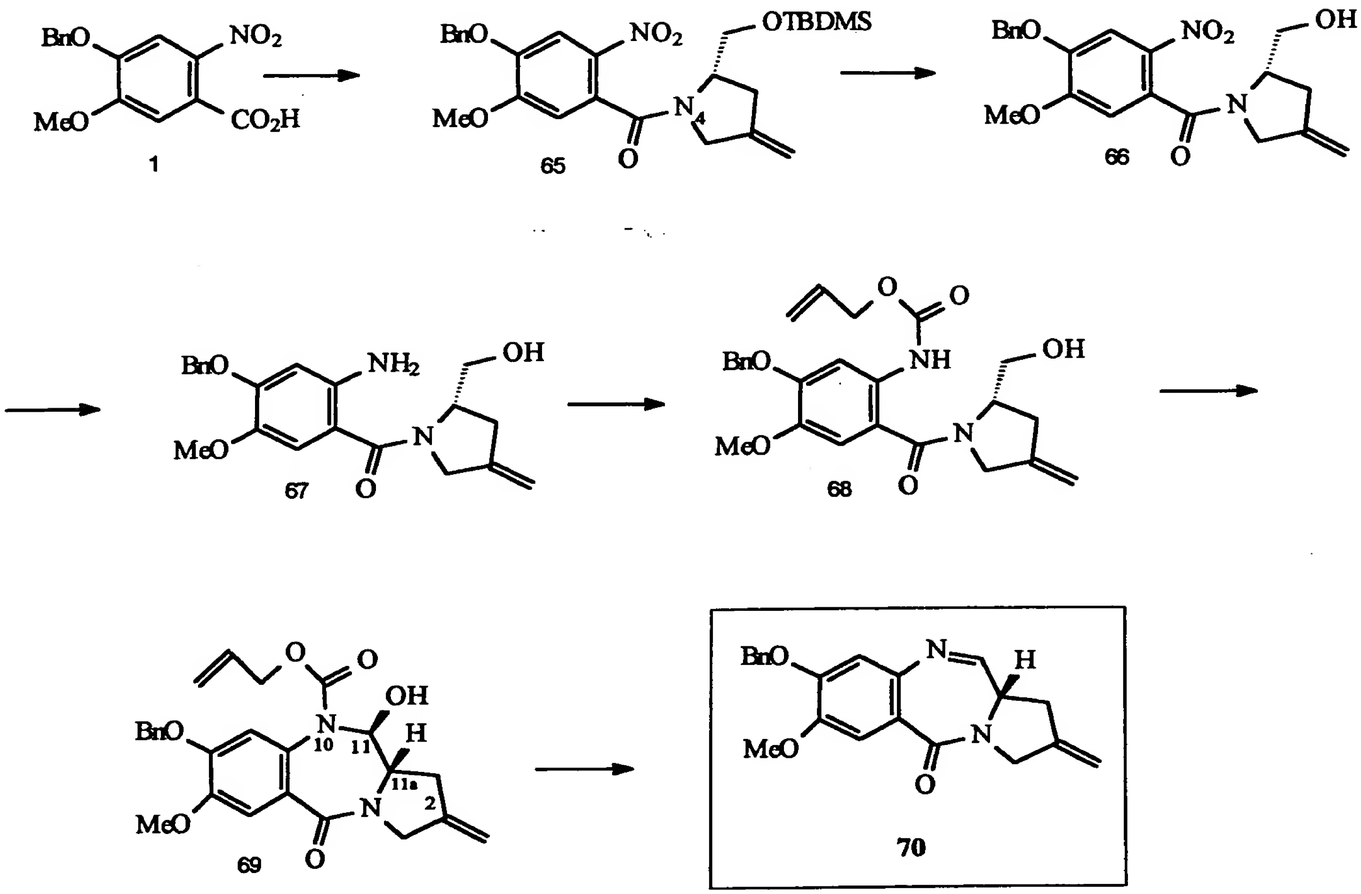
N
O
64 (BSD-SJG, UP-2023)

Figure 7


BnO
NO2
MeO
CO2H
1
OTBDMS
N4
O
65
OH
N
66
NH2
67
O
NH
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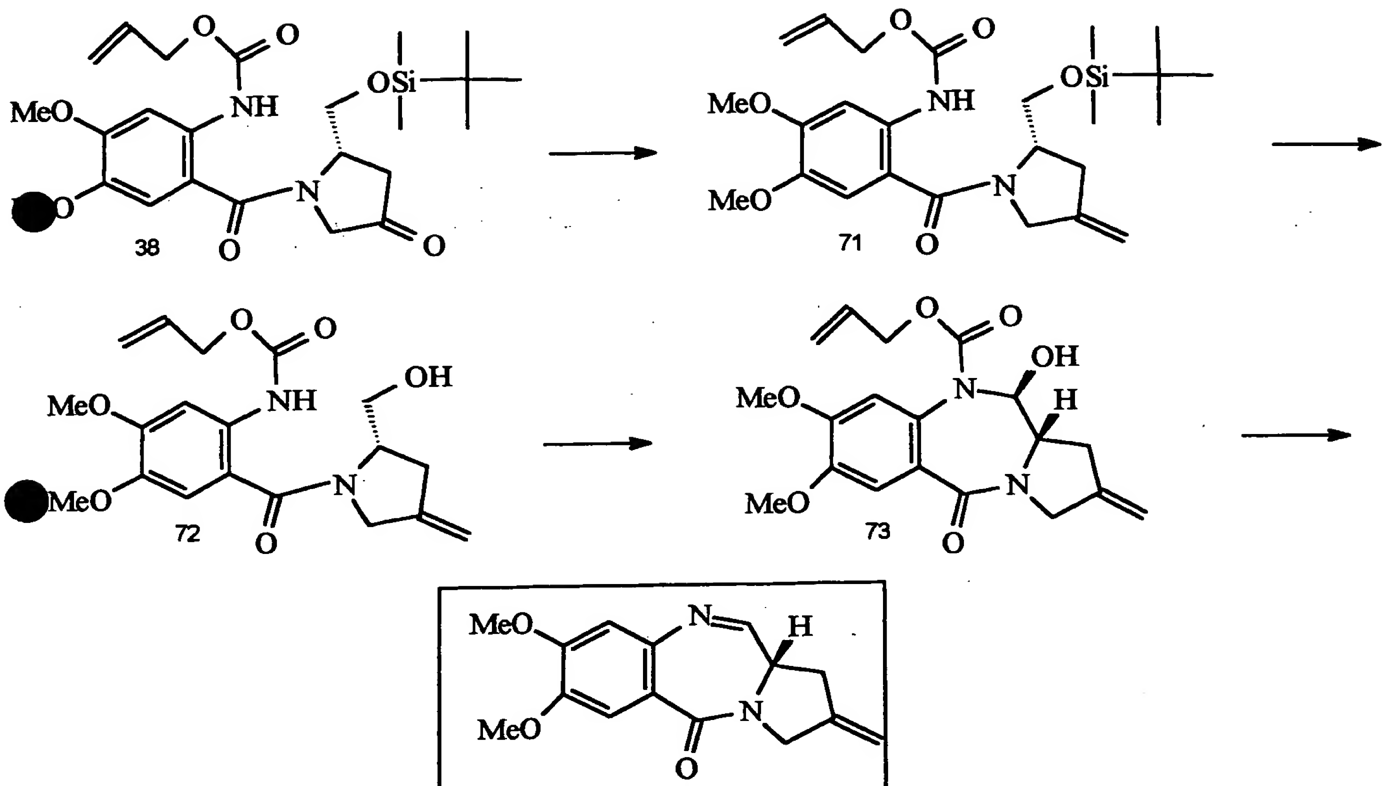
10
11
H
11a
2
69
N
H
70

Figure 8



74 (MMY-SJG, UP2064)

Figure 9

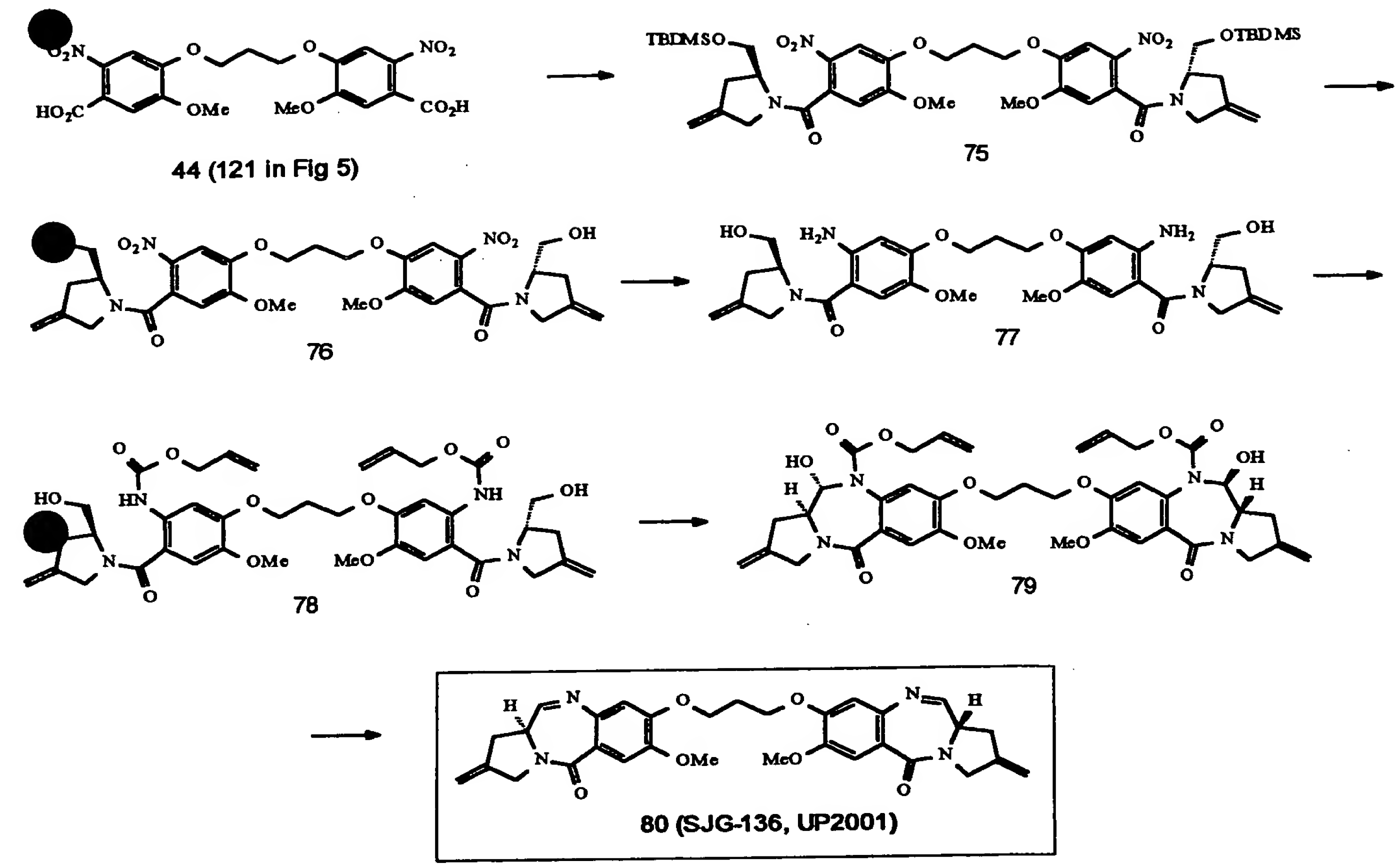


Figure 10

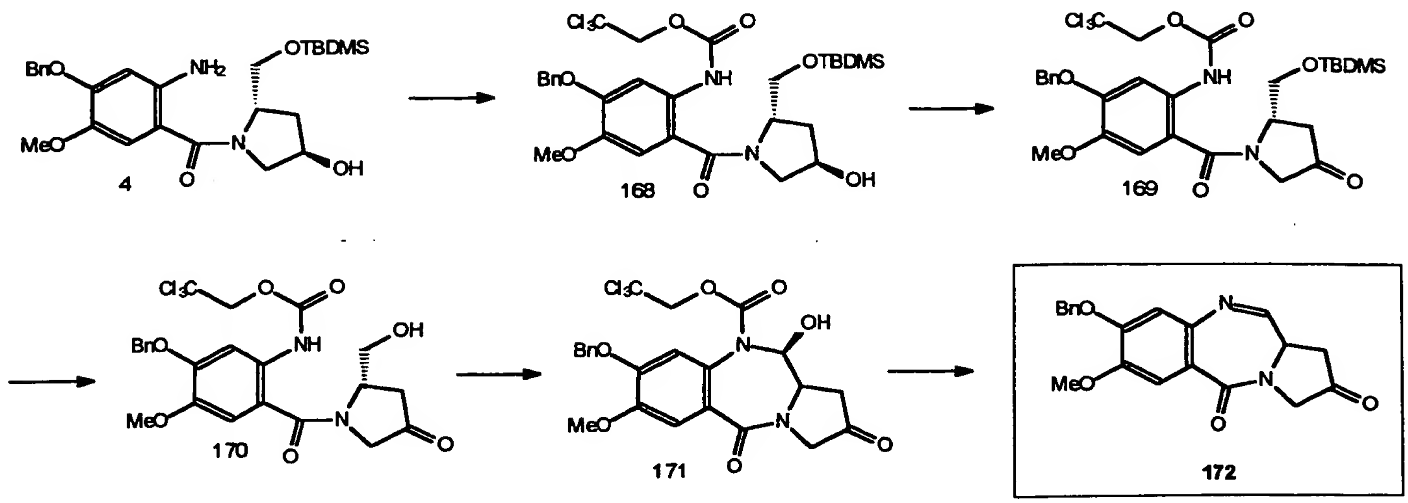
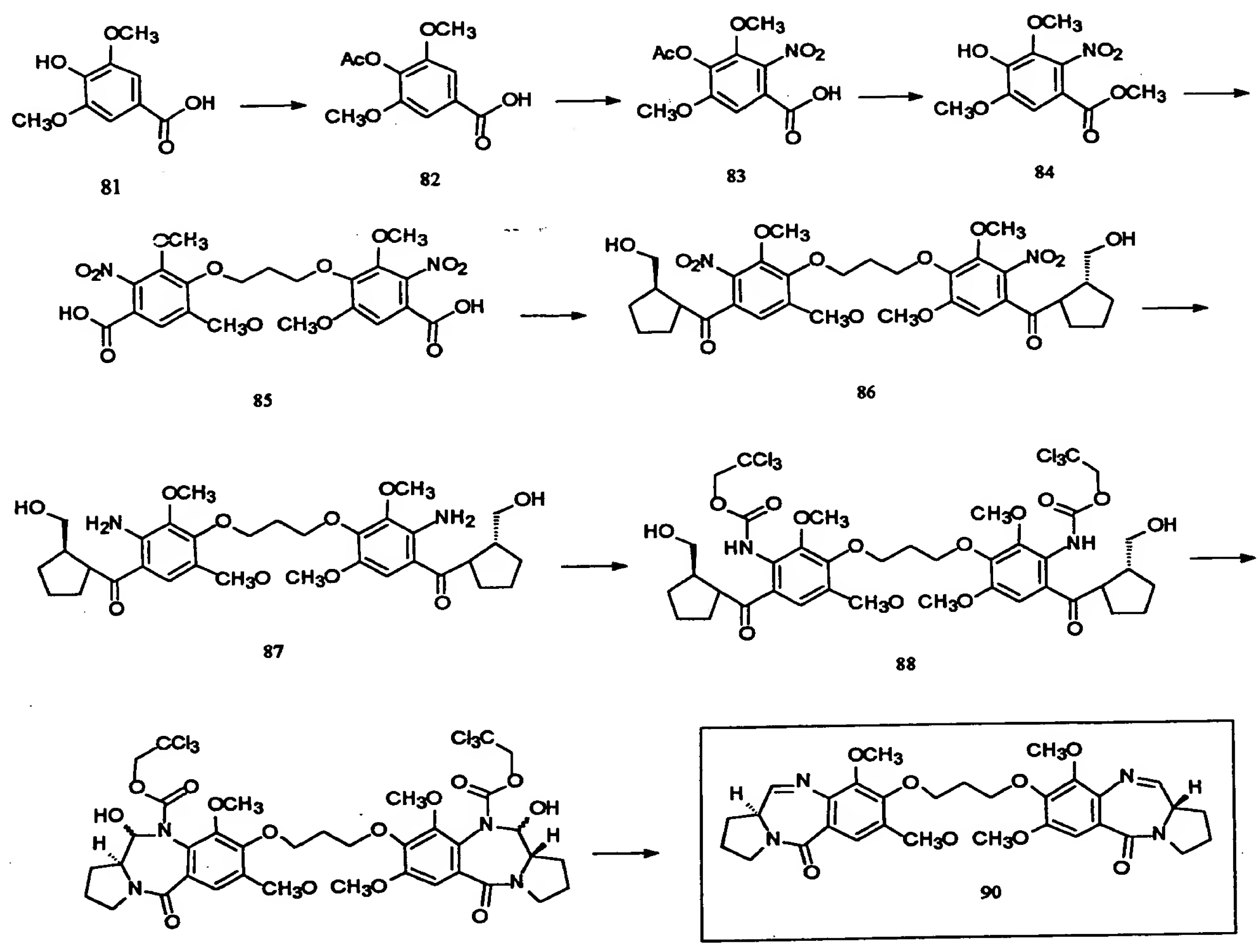


Figure 11



81 82 83 84 85 86 87 88 89 90

Figure 12

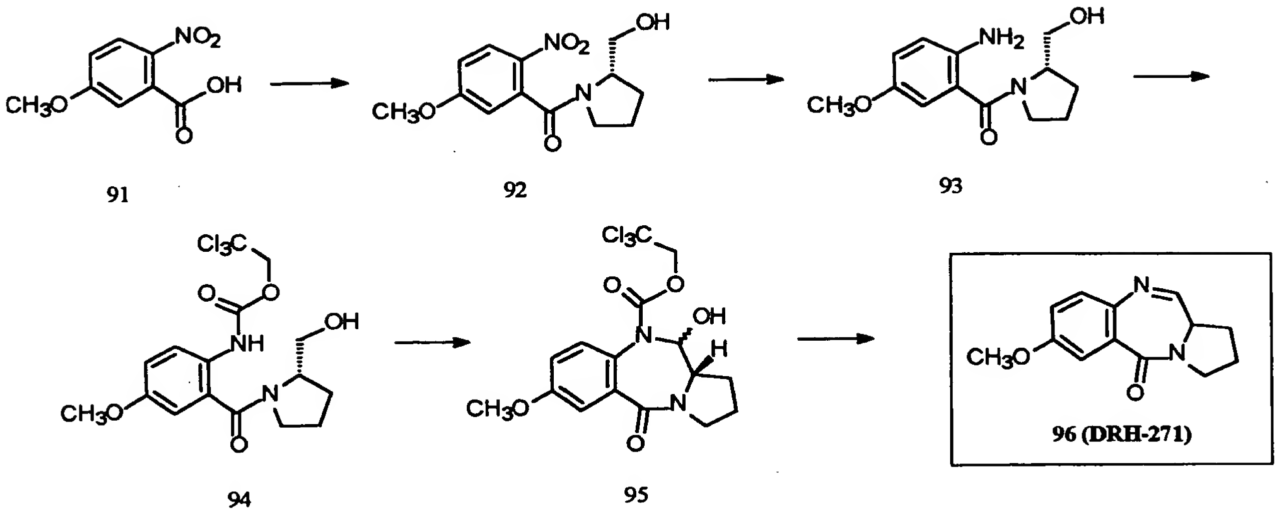
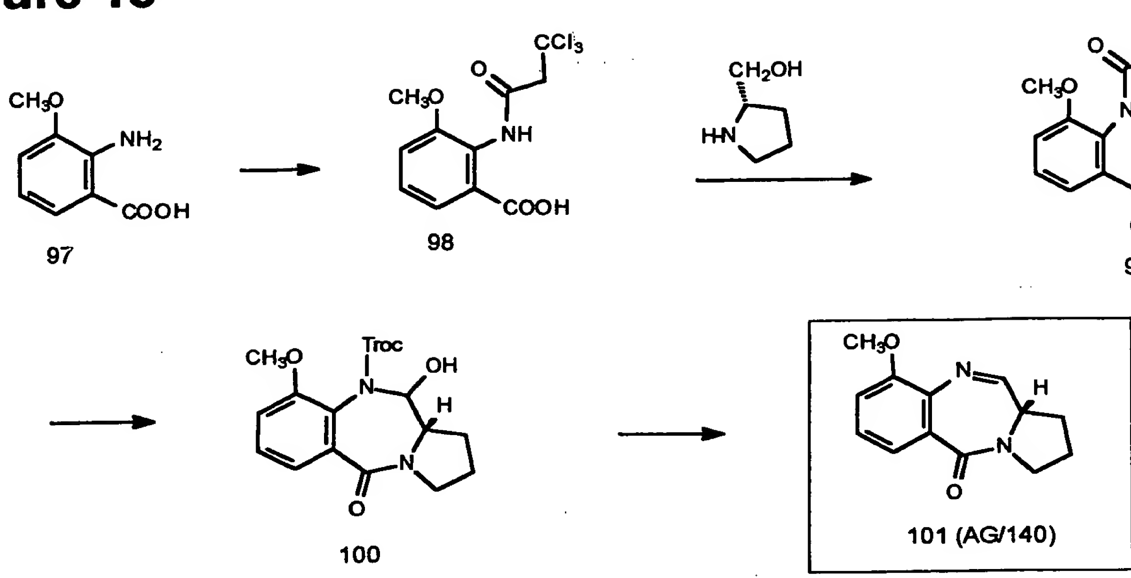


Figure 13



97 98 99 100 101 (AG/140)

Figure 14

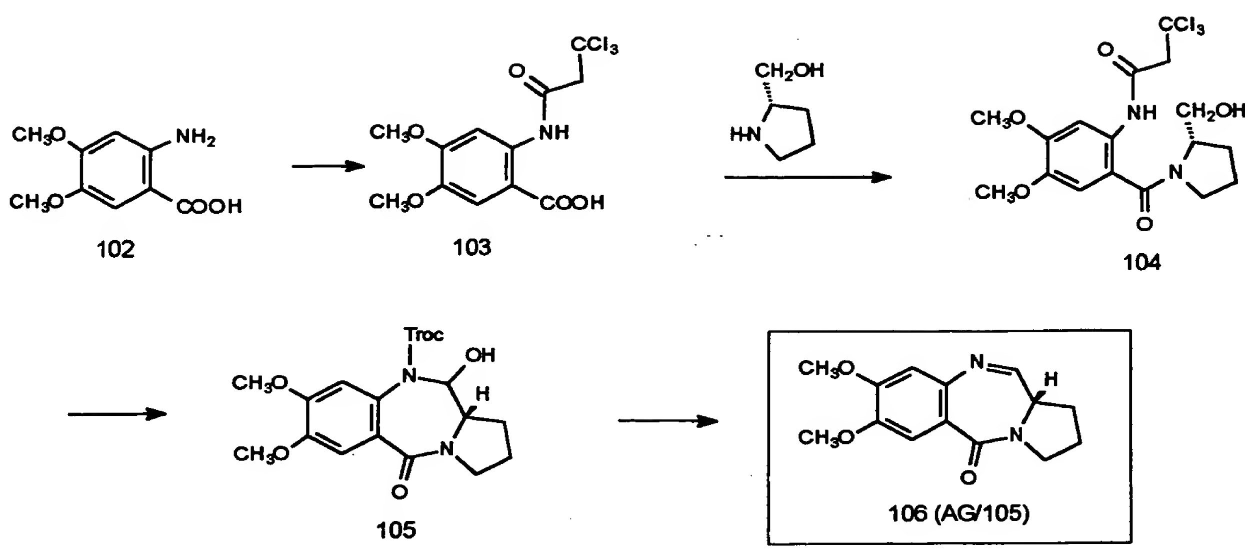
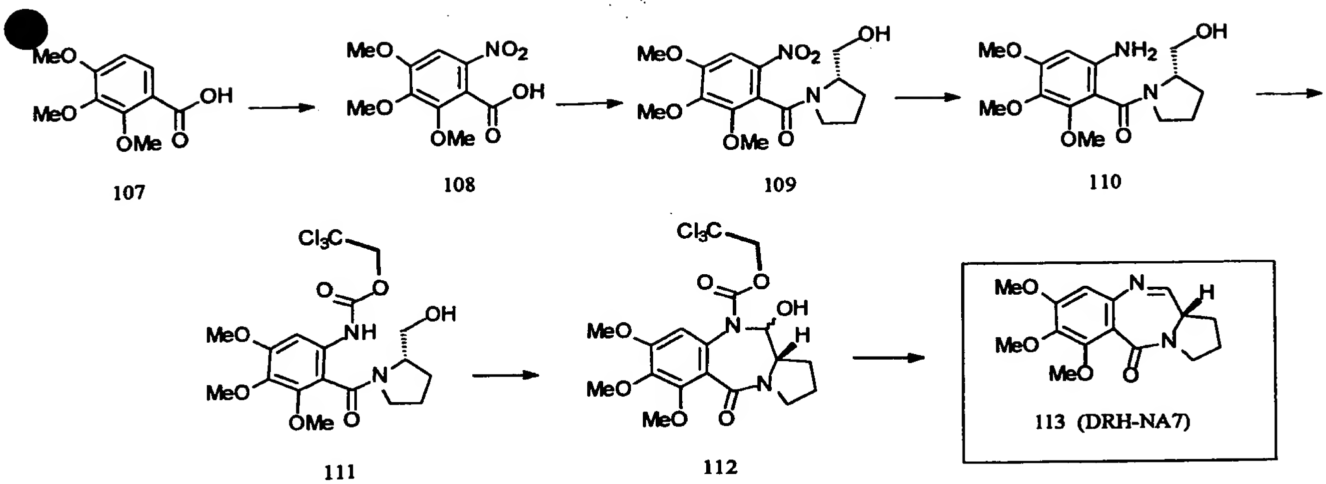

CH3O
NH2
CH3O
COOH
102
CCl3
O
NH
COOH
103
CH2OH
HN
CH2OH
N
O
104
Troc
N
OH
H
N
O
105
N
H
N
O
106 (AG/105)

Figure 15



107 → 108 → 109 → 110 → 111 → 112 → 113 (DRH-NA7)

Figure 16

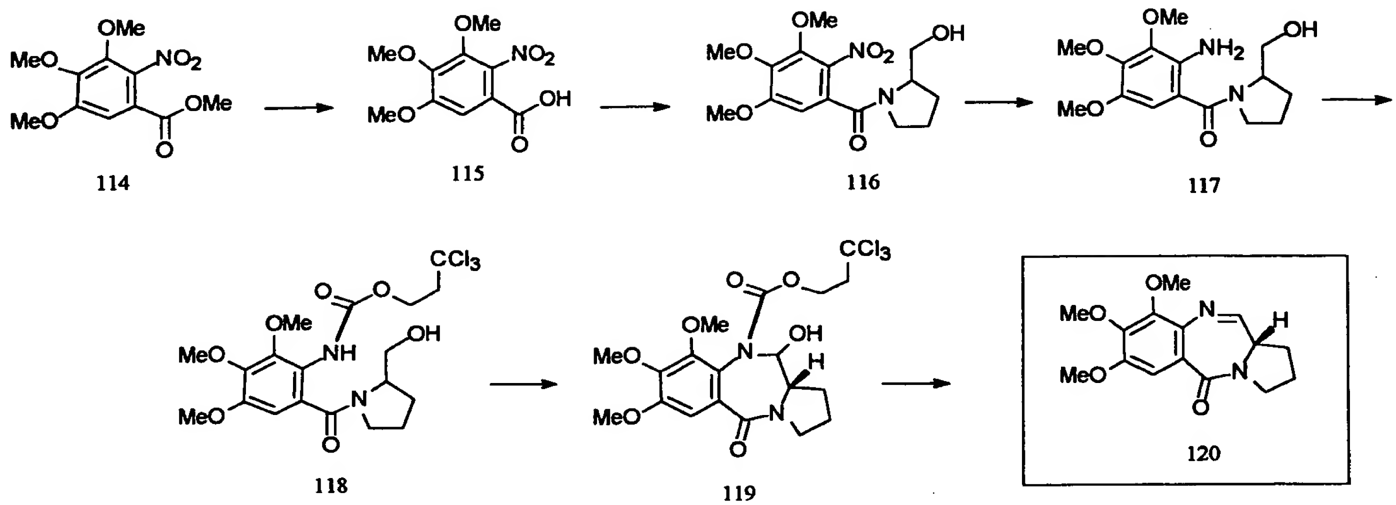

OMe
MeO
NO_2
MeO
OMe
O
114
OH
115
N
116
NH_2
117
CCl_3
NH
118
H
119
120

Figure 17

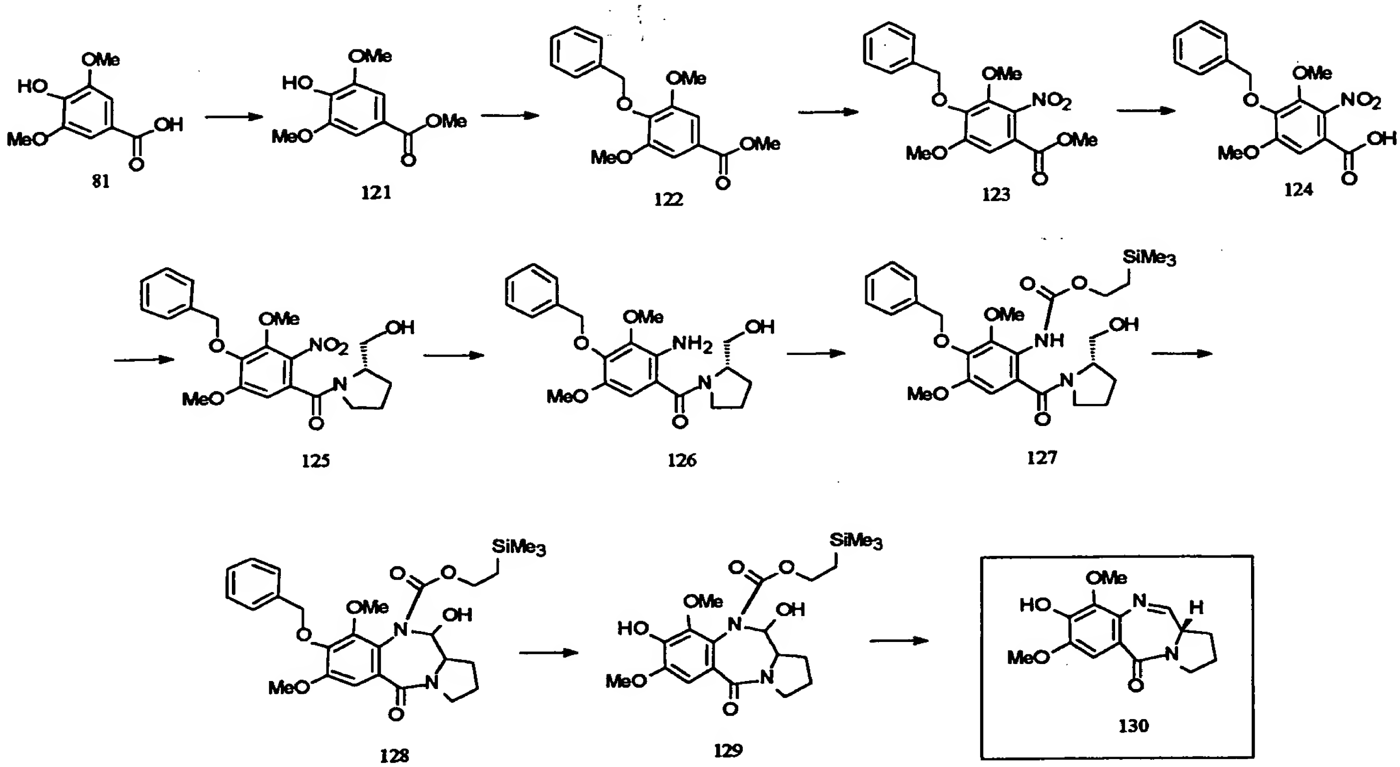
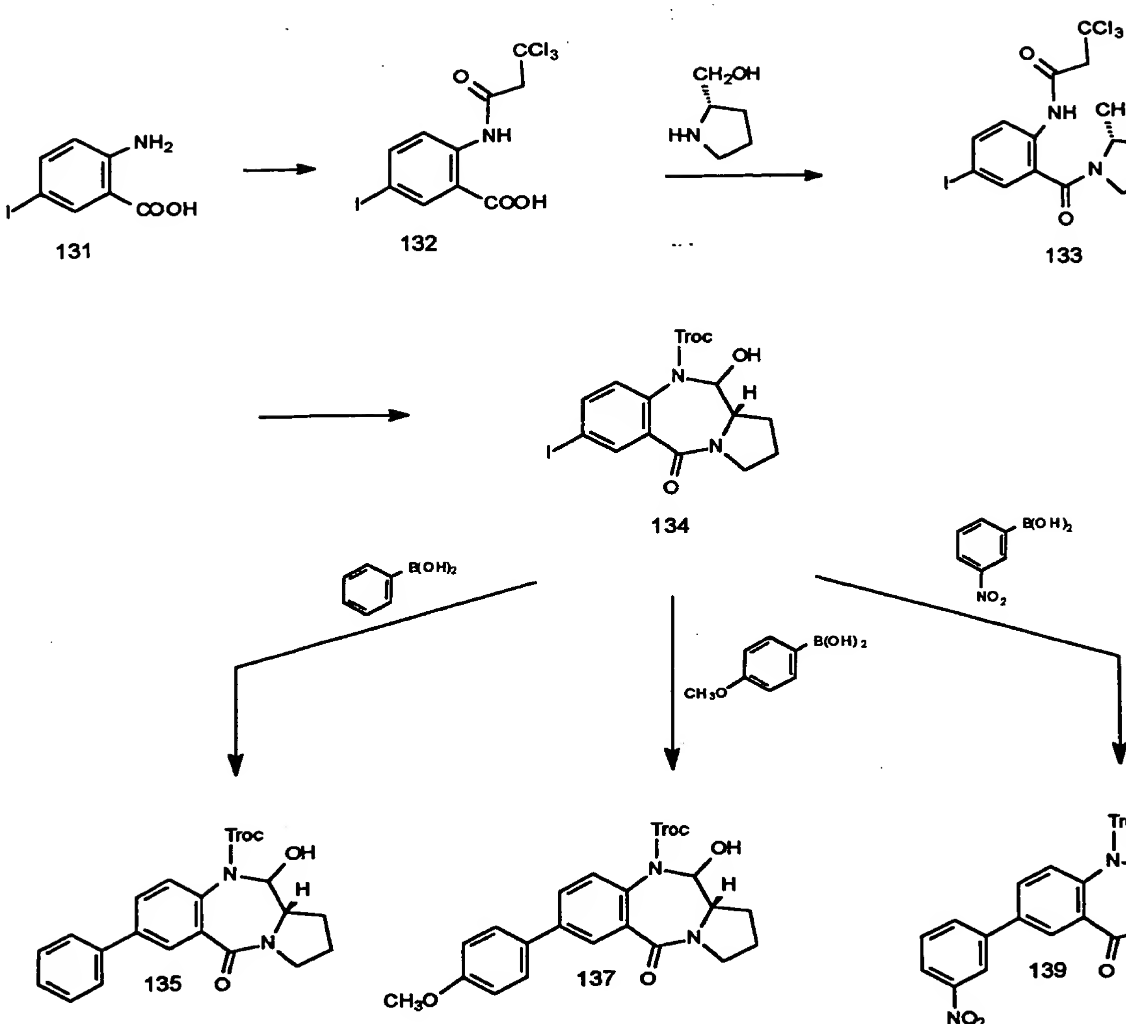
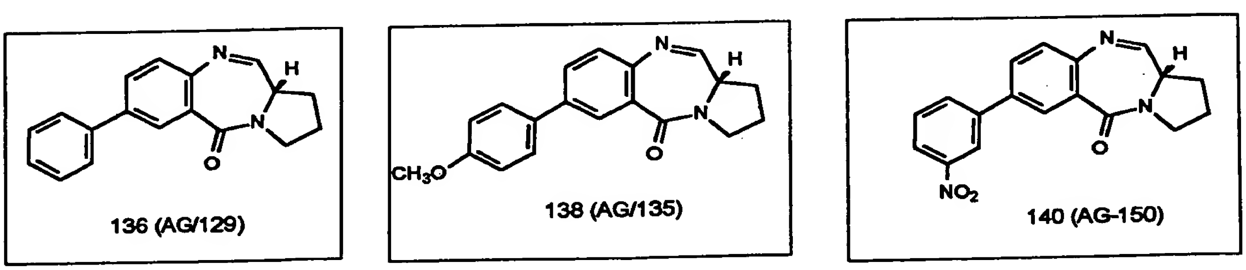


Figure 18



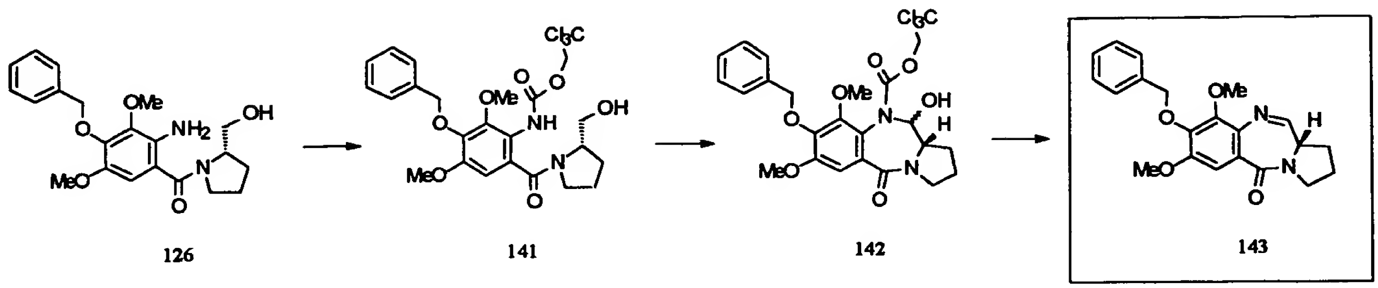


136 (AG/129)

138 (AG/135)

140 (AG-150)

Figure 19



126 141 142 143

Figure 20

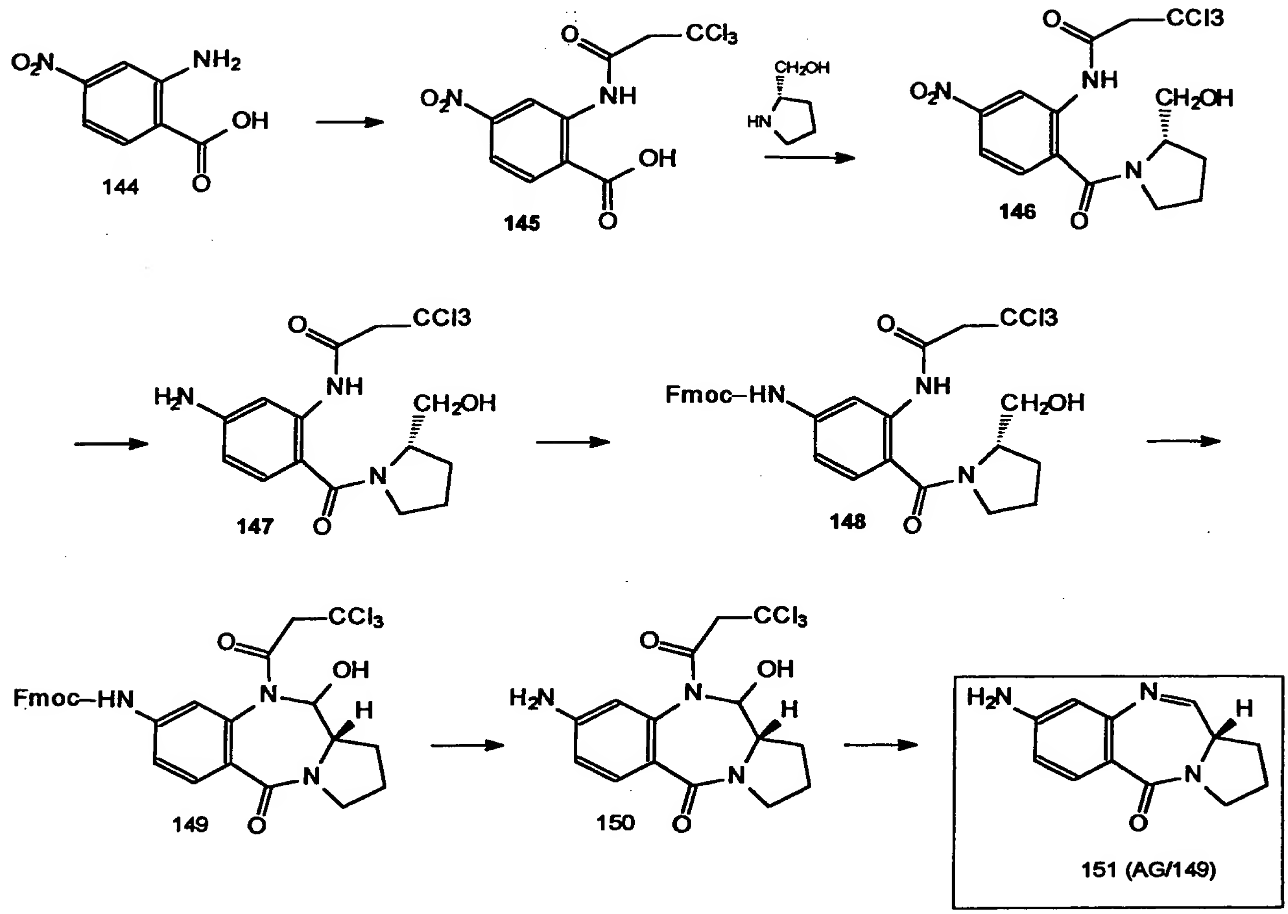
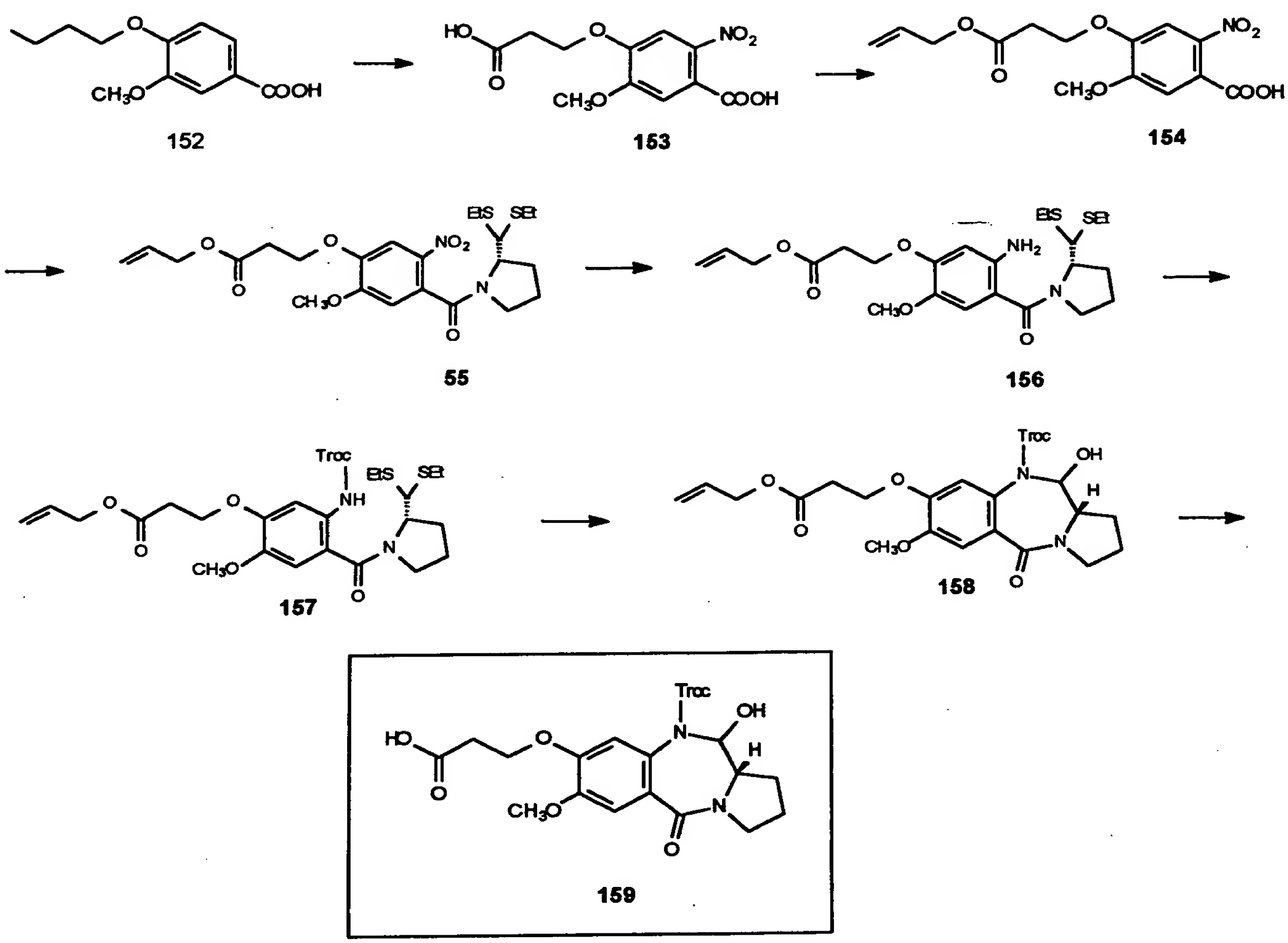

O2N
NH2
OH
O
144
CCl3
O
NH
OH
145
CH2OH
HN
CCl3
CH2OH
N
146
H2N
147
Fmoc-HN
148
OH
H
149
150
151 (AG/149)

Figure 21



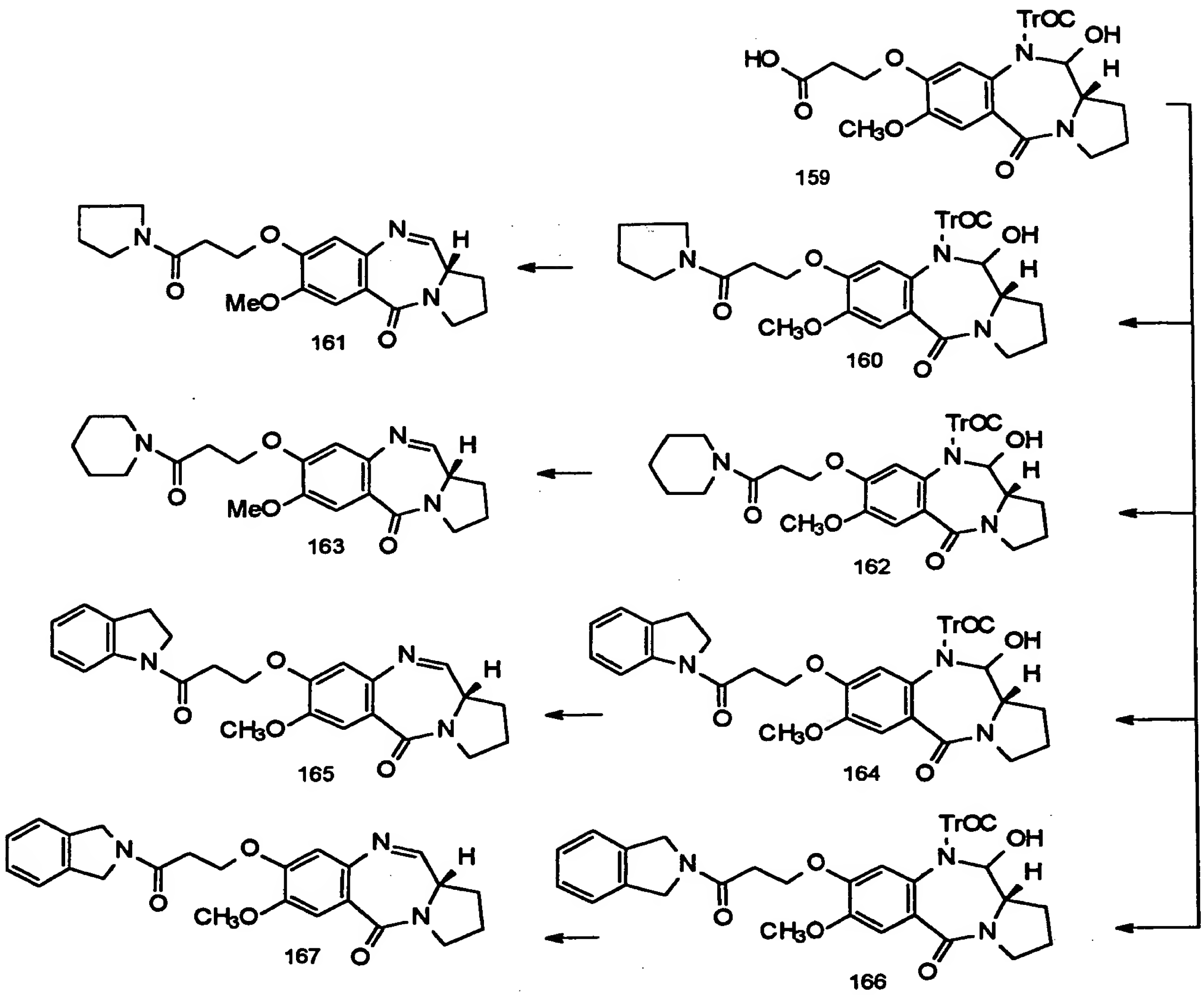
152 153 154

55 156

157 158

159

Figure 22



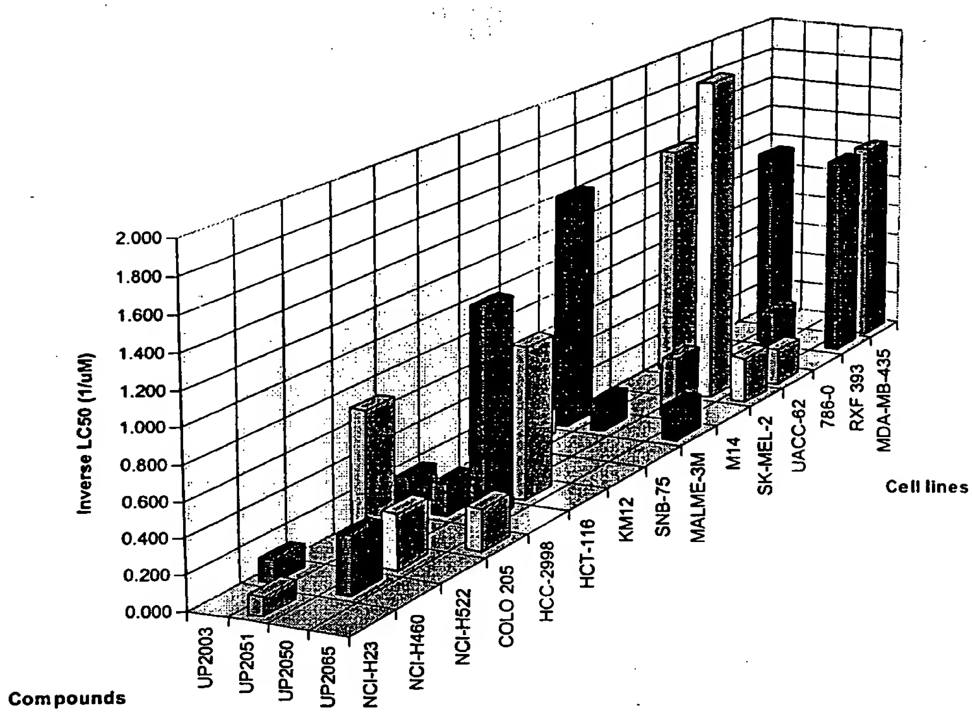


Figure 23

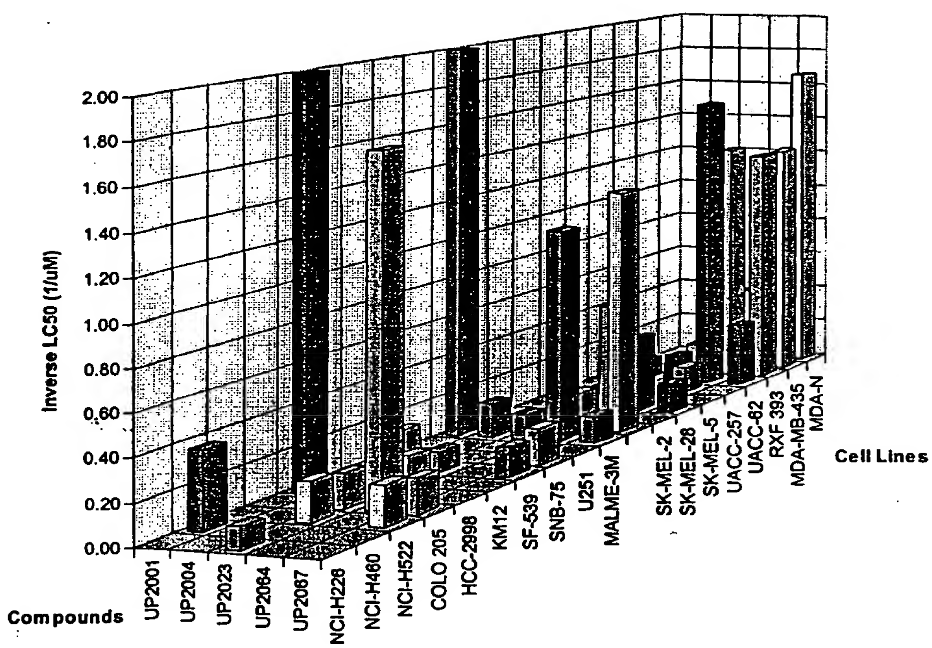


Figure 24

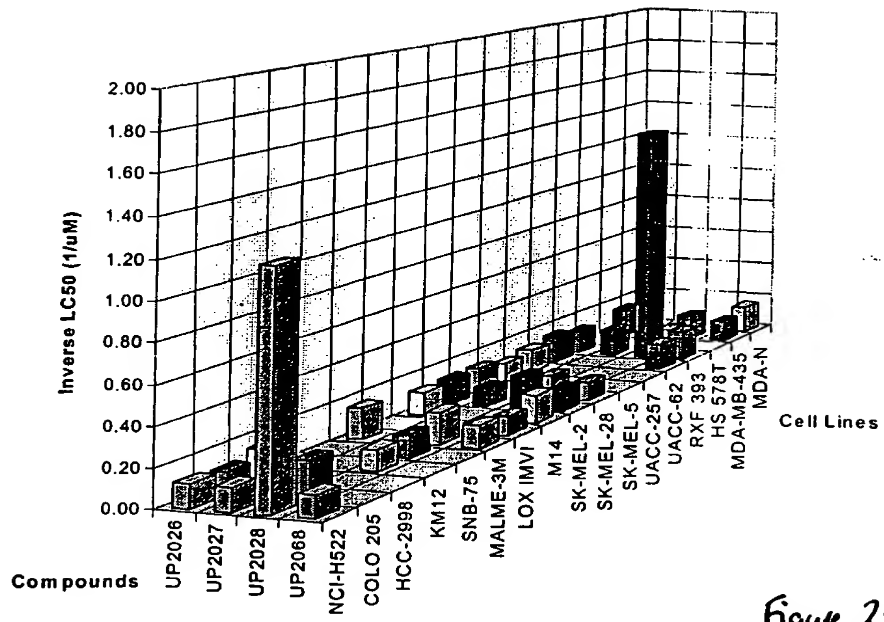


Figure 25

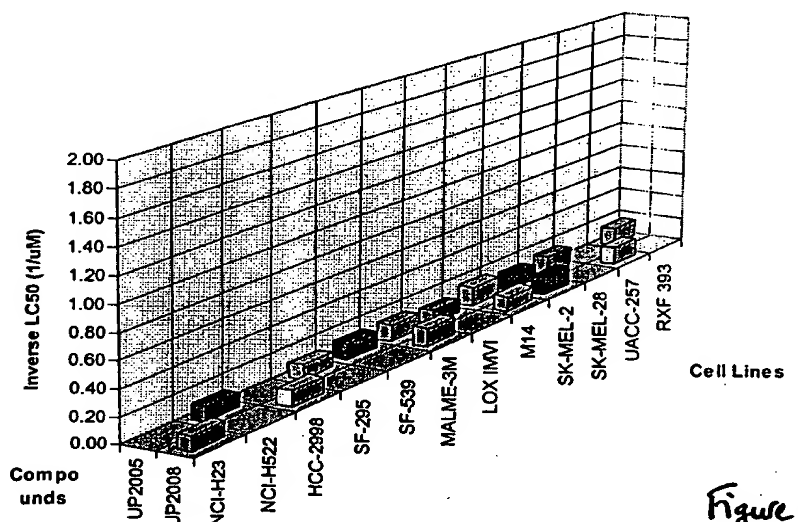


Figure 26

PCT NO : GB99/02838

FORM 23/77 : 27/8/99

AGENT Mewburn Ellis